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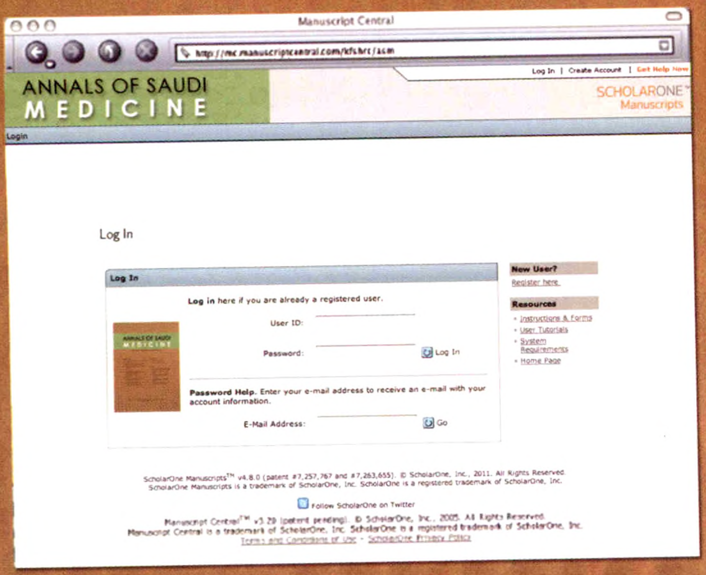
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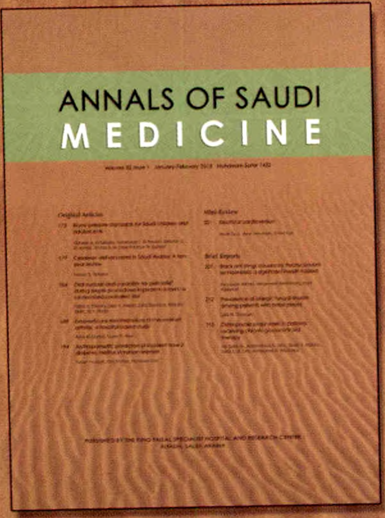

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Orthopedic Basic Science Course
10-12 January 2012 / 16-18 Safar 1433
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5th KFSH&RC Residents' Research Day
11 January 2012 / 17 Safar 1433
Contact No.: 4647272 Ext 31730 (Research Center)

FEBRUARY

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Contact No. 464-7272 Ex. 38499 (Radiology)

2nd Pediatric Flexible Bronchoscopy Course
19-22 February 2012 / 27-30 Rabi Al Awal 1433
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International Conference in Radiation Medicine
27 Feb – 01 Mar 2012 / 05-08 Rabi Al Thani 1433
Contact No. 442-7897 (Research Center)

MARCH- APRIL

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03-04 March 2012 / 10-11 Rabi Al Thani 1433
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Update on Perinatal Diagnosis and Fetal Therapy Workshop
06-07 March 2012 / 13-14 Rabi Al Thani 1433
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2nd International Conference on Pediatric Emergency Medicine
13-15 March 2012 / 20-22 Rabi Al Thani 1433
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Evidence Based Practice Workshop
17-19 March 2012 / 24-26 Rabi Al Thani 1433
Contact No.: 464-7272 Ext. 31538 or Ext. 39073 (Quality Management)

Systematic Review Course
20-21 March 2012 / 27-28 Rabi Al Thani 1433
Contact No.: 464-7272 Ext. 31538 or Ext. 39073 (Quality Management)

Saudi Colorectal Surgery Forum
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Contact No.: (Surgery)

Future of Prevention of Genetic Diseases in KSA: New KFSH&RC Initiative
04 April 2012 / 12 Jumada Al Awal 1433
Contact No.: 4424988 (Medical Genetics)

3rd Urodynamic Course
07 April 2012 / 15 Jumada Al Awal 1433
Contact No.: 442- 4302 (Urology)

Updates in Nuclear Medicine and Molecular Imaging Symposium
10-11 April 2012 / 18-19 Jumada Al Awal 1433
Contact No.: 464-7272 Ext. 38587 (Radiology)

2nd Musculoskeletal Oncology Symposium
17-19 April 2012 / 25-27 Jumada Al Awal 1433
Contact No.: 464-7272 Ext. 31830 or 442-7591 (Orthopedic Surgery)

OR INFORMATION :
Please contact the numbers listed for each activity or visit our Website: www.kfshrc.edu.sa/symposia

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Oncology Centre Academic & Research Day
02 May 2012 / 11 Jumada Al Thani 1433
Contact No.: 4647272 Ext 38005 (Oncology Center)

Recent Advances in Surgical Pathology from Morphology to Molecular Diagnosis Symposium
15-17 May 2012 / 24-26 Jumada Al Thani 1433
Contact No.: 464-7272 Ext. 31830 or 442-4251 (Path & Lab Medicine)

9th Annual Academic Day
23 May 2012 / 02 Rajab 1433
Contact No.: 4423934 (Pediatric Hematology / Oncology)

JUNE

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08-10 October 2012 / 22-24Dhu Al Qada 1433
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Physical Therapy, Occupational Therapy, Speech Therapy and Prosthetics Conference
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Contact No.: 464-7272 Ext. 31830 or 442-3892 (Physical Therapy)

NOVEMBER

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18-21 November 2012 / 04-07 Muharram 1434
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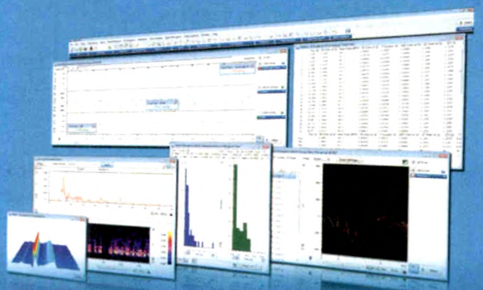

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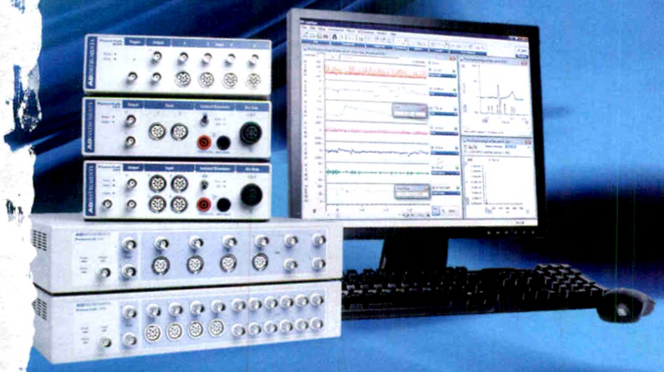

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SUMMARIES

MEDICAL GENETICS

A molecular analysis of familial Mediterranean fever disease in a cohort of Turkish patients

In a retrospective study, Dundar and colleagues found that of 446 patients with FMF, half (221 patients) had the MEFV mutations. High parenteral consanguinity rates affect FMF development.

Association of interleukin 4 (-590 T/C) and interleukin 4 receptor (Q551R A/G) gene polymorphisms with acne vulgaris

In a case-control study of 95 patients with acne vs 87 normal controls, Robaee and colleagues found a highly significant difference in the IL-4R (Q551R A/G) gene, and data indicating that these polymorphisms are associated with the susceptibility rather than severity of acne vulgaris.

ONCOLOGY

De novo malignancies after liver transplantation: a single-center experience

In a retrospective study, Hegab and colleagues found that 8 (3.4%) of 238 liver transplant patients developed malignancies after surgery. EBV-associated post-transplant lympholiferative disorders were most frequently encountered.

Intracranial germ cell tumors: A single-institution experience

In a retrospective study of 57 patients over the period 1985 to 2007, Khafaga and colleagues found that overall, event-free and relapse-free survival was much better for germinoma versus non-germinomatous germ cell tumors. For the latter, younger age, higher tumor dose of radiation and later year of diagnosis (after 1990) favorably affected outcome.

CARDIOLOGY

Are acute coronary syndrome patients admitted during off-duty hours treated differently? An analysis of the Saudi Project for Assessment of Acute Coronary Syndrome (SPACE) study

In a prospective study of 2825 patients admitted with ACS, Al Faleh and colleagues found that patients admitted during off-duty hours were more likely to have heart failure and ST elevation MI were more likely to receive fibrinolytic therapy but less likely to undergo primary percutaneous coronary interventions. No differences were observed in hospital outcomes including mortality.

Incidence of ventricular arrhythmia and associated patient outcomes in hospitalized acute coronary syndrome patients in Saudi Arabia: findings from the registry of the Saudi Project for Assessment of Acute Coronary Syndrome (SPACE)

In a prospective study of 5055 ACS patients enrolled in the SPACE registry, Hersi and colleagues found that remarkedly higher rates of adverse events and greater mortality were associated with in-hospital VA. Risk factors were male gender and lower systolic blood pressure.

The relationship between coronary artery calcification and myocardial perfusion in asymptomatic women

In a prospective study of 101 women without known CAD, Fathala and colleagues found that the presence of coronary artery calcification was the most important predictor of myocardial perfusion scintigraphy results indicating subclinical CAD. They conclude that CAC screening is an appropriate initial test for CAD in asymptomatic women.

Relationship between obstructive sleep apnea severity index and left ventricular function and volume

In a cross-sectional study involving 40 patients with OSA, Altintas and colleagues found they cardiac abnormalities worsened with severity of apnea. They concluded that the myocardial performance index may serve as a surrogate outcome measure in assessing these patients.

DIABETES

The relationship between markedly elevated glucose challenge test results and the rate of gestational diabetes mellitus and gestational impaired glucose tolerance

In a retrospective study, Karcaaltincaba and colleagues found that a GCT result of 200 mg/dL was an ideal cutoff value for the diagnosis of GDM and GIGT in patients 35 years and older. The OGTT can be omitted in these patients.

QUALITY OF LIFE

Health-related quality of life of Saudi hepatitis B and C patients

Abdo prospectively collected quality of life information on 250 consecutive patients (107 with hepatitis B and 113 with hepatitis C) who completed an SF-36 questionnaire. Hepatitis C patients had significantly lower scores in several domains.

FAMILY MEDICINE

Puberty development among children and adolescents with chronic disease in Saudi Arabia

In a cross-sectional study, AlBuhairan and colleagues found that the age of onset of pubertal development in 115 children (11.3% of students surveyed) with chronic illness was within normal limits. Fifty-three (34%) of the 115 children were overweight or obese.

DERMATOLOGY

Pattern of patch test reactivity among patients with clinical diagnosis of contact dermatitis: a hospital-based study

Of 196 patients referred to an allergy clinic over 2 years, Almogren and colleagues found that 91 cases (46.4%) had a positive reaction to one or more allergens. The highest reactivity was to nickel sulfate, which is common in many products including earrings and pins. They emphasize the need to formulate policies towards avoidance of these contact allergens.

original article

A molecular analysis of familial Mediterranean fever disease in a cohort of Turkish patients

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BACKGROUND AND OBJECTIVES: Familial Mediterranean fever (FMF) is an autosomal recessive disorder caused by mutations in *MEFV* gene, which encodes pyrin. FMF is especially prevalent among Turks, Armenians, non-Ashkenazi Jews, and Arabs. The aim of this study was to determine the frequency and spectrum of 12 *MEFV* mutations of these patients and any genotype-phenotype correlation in this large Turkish group.

DESIGN AND SETTING: A retrospective study at Erciyes University Medical Faculty, from January 2007 to June 2009.

PATIENTS AND METHODS: We enrolled 446 Turkish FMF patients and identified the known 12 MEFV mutations with clinical investigations. DNA was amplified by PCR and subjected to reverse hybridization for the detection of MEFV gene mutations.

RESULTS: Among the 446 patients, 103 (46.6%) had a heterozygous genotype, 44 (19.9%) had a homozygous-genotype, and 74 (33.49%) had a compound heterozygous genotype. The most common mutation detected was heterozygote M694V (46/221). Of the included 446 patients, 218 (48.87%) were male and 228 (51.12%) were female. High parental consanguinity rates affect FMF development. The clinical spectrum varied with different mutation profiles.

CONCLUSIONS: This study plays an important role in detecting the distribution of *MEFV* mutations and determining clinical approaches among Turk FMF patients. Also, we seemed to detect a distinctive clinical picture, specifically a lower frequency of amyloidosis.

Familial Mediterranean fever (FMF) is an autosomal recessive, systemic inflammatory disorder characterized by unprovoked recurrent, self-limited episodes of fever; and serosal, synovial, or cutaneous inflammation attacks with abdominal pain, pleuritis, and arthritis.[1,2] FMF is a disease that is especially seen in several eastern Mediterranean populations, like Turks, Sephardic Jews, Armenians, and Arabs.[3] The carrier frequency of the disease is approximately 1 per 8-16 individuals. The estimated prevalence of FMF in Turkey is 1/1000, and carrier rate is 1/5.[4] Peritoneal and pleural inflammation, arthritis, erysipelas-like erythema, and arthralgia are well-known features of FMF and may vary in different populations.[5] Arthritis occurs more frequently in Jews than in Turks, Arabs, and Armenians.[6]

The gene is located on chromosome 16p13.3 and includes 10 exons and encodes a 781-amino acid protein named pyrin or marenostrin.[7] The pyrin protein is associated with the interleukin-1 (IL-1)-related inflammatory reactions and is involved in the regulation of apoptosis and inflammation. The *MEFV* transcript, which plays an essential role in the inflammatory response, is expressed in granulocytes. Recently obtained data revealed over 70 different mutations in FMF patients. These are grouped as missense, nonsense, and deletion mutations. Most of the mutations are localized in a small part of exon 10.[8,9] Four common mutations in exon 10 (M694V, M694I, V726A, and M680I) and onemutation in exon 2 constitute 85% of the known mutations in geographical areas where FMF is frequent.[10] In recent studies, it was seen that the severity of the disease is affected by environmental factors, and *MEFV* mutations are not the only cause of the disease.[6,11]

In the clinical approach, the FMF patients are divided into two subgroups: phenotype 1 and phenotype 2. In phenotype 1, only attacks of serosal inflammation are reported. In phenotype 2, only amyloidosis is present and no other clinical manifestations are reported.[12] Reactive or secondary AA amyloidosis is seen in FMF patients as a severe complication. The amyloid slowly accumulates in various organs and tissues; organ dysfunction follows this period. Renal amyloidosis is especially common in Turks.[13] Colchicine has been used for the prevention of the disease and has been shown to markedly change the clinical course of the disease (especially the development of amyloidosis).[14] The objective of this study was twofold: (1) to determine the frequency of the 12 mutations of the *MEFV* gene in a large FMF cohort, medical treatment, treatment response, and association with the family history; and (2) to determine the genotype-phenotype correlation between the mutation types and clinical course of the disease in the Turkish population around middle Anatolia.

PATIENTS AND METHODS

The study group comprised 446 unrelated patients (age range, 1-70 years; 218 male and 228 female) who were diagnosed as having FMF by Fonnesu and colleagues.[15] They were referred to our clinic for FMF mutation analysis between January 2007 and June 2009. This retrospective study was approved by the Erciyes University Medical Faculty, and informed consent was obtained from all the participants. The study was performed in Middle Anatolia, Turkey, with the collaboration of the Department of Medical Genetics and the Department of Gastroenterology of Erciyes University Medical Faculty. Molecular test results of each and every patient were obtained; 2 mL of peripheral blood sample of each patient with EDTA was used for DNA extraction. A commercially available strip test assay (FMF strip assay; ViennaLab, www.viennalab.com) was used in the diagnosis of FMF and determination of its 12 common mutations. According to the FMF strip test method, multiplex PCR was performed using biotinylated primers for the amplification of exons 2, 3, 5, and 10. Investigated mutations were as follows: E148Q in exon 2; P369S in exon 3; F479L in exon 5; and M680I (G/C), M680I (G/A), I692del, M694V, M694I, K695R, V726A, A744S, and R761H in exon 10. Hybridization of PCR products to the strip absorbed immobilized wild type and mutated oligonucleotide probes. Hybridization was performed in an automated incubator (AutoLIPA; Innogenetics, Belgium). Hybridizations were illuminated by the reaction of streptavidin-alkaline phosphatase and color substrate.

Mutation results are given in percentages. Categorical variables were compared using the chi-square test. Also, the Fisher exact test was used to compare the values. $P<.05$ was considered statistically significant.

RESULTS

In the study group, comprising patients referred to our clinic for FMF testing, 225 had no definable mutations. One hundred three (46.6%) of the subjects were carrying at least 1 mutated *MEFV* allele. The frequencies of M694V, E148Q, M680I (G/C), and V726A mutation carriages were 20.81%, 9.5%, 7.23%, and 4.97%, respectively. Forty-four (19.9%) subjects had the homozygous genotype and 74 (33.49%) had the compound heterozygous genotype. All the homozygous patients were from consanguineous families. Heterozygous M694V (46/221), compound heterozygous M694V/M680I (G/C) (27/221), homozygous M694V (25/221), and heterozygous E148Q (21/221) mutations were significantly common in the mutation carrier group (**Table 1**). The allele frequencies of the most common mutations were M694V, 15.8%; M680I (G/C), 8.85%; E148Q, 5.15%; and V726A, 4.14% (**Table 2**).

Of the 446 patients, 48.87% were male (n=218) and 51.1% were female (n=228) (female-to-male ratio, 1.04:1). The main clinical characteristics were as follows: abdominal pain was observed in 353 (79.1%) patients; fever, in 230 (51.6%) patients; arthritis, in 138 (30.9%) patients; and erysipelas-like erythema, in 24 (5.4%) patients. The clinical characteristics, such as abdominal pain, arthritis, and fever, were more prevalent in females than in males , and the female-to-male ratio was, respectively, 55/45, 61/38, and 59/41.

FMF patients were divided into two groups, female and male (see **Tables 3 and 4**), and these groups were compared according to ages and mutation types. Genotype distribution according to gender was as follows: the non-carrier group was more prevalent among females (female-to-male ratio: 49.56/45.41), compound heterozygotes were more prevalent among males (21.10%), and the *MEFV*-mutated allele–carrying rate was higher among males as compared to females (males, 54.59%; females, 50.44%). When the groups were compared, significant regional differences were observed in mutation-carrying profile in Kayseri and other cities. Especially, heterozygous mutation-carrying rates were higher in Kayseri than other mutational forms.

As a complication, amyloidosis developed in 17 (3.81%) patients. Appendectomy was performed in 47 (10.5%) patients, mostly for compound heterozygous mutations; and cholecystectomy was performed in 11 (2.5%) patients, mostly for compound heterozygous mutations. Of the included cases, 29 patients had an operation history without any mutation profile; in addition, 19 patients had a history of inoperable appendix pain.

Colchicine therapy was administered to 125 patients; 41 (32.8%) of them responded to the therapy, while 10 (8%) did not. Seventy-four (59.2%) of these 125 patients used both colchicine and medical supportive therapy. Colchicine treatment response and mutational comparisons are summarized in **Table 5**. M694V homozygous (n=3; 12.5%) and compound heterozygous (n=3; 12.5%) states were also found in patients with erysipelas.

Table 1. Distribution of the MEFV gene mutations.

Mutation	Genotype	Number (n=221)	%
Heterozygotes (n=103) (46.6%)	M694V	46	20.81
	E148Q	21	9.5
	M680I (G/C)	16	7.23
	V726A	11	4.97
	R761H	4	1.8
	K695R	3	1.3
	P369S	1	0.45
	A744S	1	0.45
Homozygotes (n=44) (19.9%)	M694V	25	11.3
	M680I (G/C)	12	5.42
	E148Q	5	2.26
	V726A	2	0.9
Compound heterozygotes (n=74) (33.49%)	M694V/M680I (G/C)	27	12.21
	M694V/V726A	11	4.97
	M680I (G/C)/V726A	9	4.07
	M694V/E148Q	7	3.16
	M680I (G/C)/E148Q	3	1.3
	E148Q/P369S	3	1.3
	E148Q/V726A	2	0.9
	OTHERS	12	5.42

Table 2. Common MEFV mutations among the FMF-affected cohort of patients.

Mutation (221 patients)	Number of alleles	Allele frequency (%)
M694V	141	15.8
M680I (G/C)	79	8.85
E148Q	46	5.15
V726A	37	4.14

DISCUSSION

In this study, we investigated 446 patients suffering from FMF. Demographic and clinical characteristics of the FMF mutations, as well as colchicine treatment responses and the phenotype-genotype correlations, were compared in the FMF patients. The results of our study were similar to those of the other researchers, with the observation that M694V homozygous patients had a more severe clinical course of the disease, and the M694V mutation had a higher frequency when compared with other mutational forms. The study also confirms the mutational heterogeneity of FMF in Anatolia.

Some differences have been reported in gene mutations of FMF in the various Mediterranean populations. The five most common mutations were M694V, M680I, M694I, E148Q, and V726A.[16,17] In various recent studies, it has been reported that 70% to 80% of the total FMF cases consisted of these five mutations.[4,18,19] In our study group, the most common mutation was M694V heterozygosity (20.81%), followed by M694V-M680I (G/C) compound heterozygosity, M694V homozygosity, E148Q heterozygosity, and M680I (G/C) heterozygosity with 12.21%, 11.3%, 9.5%, and 7.23%, respectively. We could not identify the M694I mutation in our patient group. In 2008, Solak and colleagues studied 202 FMF patients and found M694V to be the most frequent mutation among them. Other mutations such as E148Q, M680I, V726A, and M694V were described based on their frequencies.[20] Our observation of M694V as the most common mutation is in agreement with that of Solak and colleagues (2008). The M694V heterozygous form constituted 20.81% and M694V homozygous form, 11.3%. Demirkaya and colleagues[21] studied 330 patients. They reported the R761H mutation compound heterozygote form in 23 patients and also found R761H as a frequent mutation for all the Mediterranean populations. Nevertheless, Touitou did not report R761H as a frequent mutation, which is a finding similar to that reported by Demirkaya and colleagues.[18] In the present study, the R761H mutation was found in 4 patients in the heterozygous form, which is in agreement with the findings by Touitou regarding the frequency of the R761H mutation (1.8%), as seen in **Table 1**. Also, we found rates similar to those in their report. No significant differences were reported in age and mutation types between genders (*P*>.05) (**Tables 3 and 4**). Nevertheless, as seen in **Tables 3 and 4**, the

Table 3. Frequency of *MEFV* gene mutations according to age and gender among females.

Age (years) (n=228)	0-20	21-40	41-60	61-80	Total (number %)
No detected mutation	80	21	10	2	113 (49.6)
Heterozygote	26	16	2	-	44 (19.3)
Homozygote	25	3	2	-	30 (13.2)
Compound heterozygote	26	11	4	-	41 (18.0)
					228

P=.216.

Table 4. Frequency of MEFV gene mutations according to age and gender among males.

Age (years) (n=218)	0-20	21-40	41-60	61-80	Total (number %)
No detected mutation	68	27	2	2	99 (45.4)
Heterozygote	35	13	4	-	52 (23.9)
Homozygote	13	6	-	-	19 (8.7)
Compound heterozygote	30	9	5	2	46 (21.1)
Other	2	-	-	-	2 (0.9)
					218

P=.419.

Table 5. Response to colchicine therapy according to mutation forms.

	Response to colchicine therapy	
Mutation	+	-
No mutation	10	5
Heterozygote	10	-
Homozygote	6	2
Compound heterozygote	15	3
	41	10

P=.234.

main diagnostic age was approximately between 0 and 20 years. The difference in carrier rate was also not statistically significant between genders (P>.05), but the carrier rate was higher in males than in females.

In the research by Inal et al, the consanguinity rate was higher in families of FMF patients. Our study reveals a positive family history in 25% (111/446) of patients; 16% (70/446) of all patients had parental consanguinity, and this ratio was not as high as that found by Inal and colleagues (40%).[2] However, the consanguinity rate in parents who had a positive family history might be a factor affecting the development of FMF disease in some of our patients.

An increased risk of amyloidosis (12%) among M694V homozygotes was reported by different Turkish groups.[2] The relationship between FMF and amyloidosis is still obscure. Some reports demonstrated no association between genotype and phenotype and/or development of amyloidosis. In the studies by Tunca et al and Tekin et al, which were performed in the Turkish population, no relationship was shown between amyloidosis and the presence of the homozygous M694V mutation.[4,22] On the contrary, in the study by Yalcinkaya et al., the M694V mutation was found to be more frequent in Turkish FMF patients with amyloidosis.[23] In some other studies, a positive correlation was found between the M694V mutation and amyloidosis.[20,24,25] According to Pasa and colleagues,[1] amyloidosis was found in 4 of 17 patients who were homozygous for the M694V mutation (in group 1); 3 of 34 patients had compound heterozygosity with M694V/other forms (in group 2). In our study, we detected 17 patients with amyloidosis, and development of amyloidosis was not found to correlate with disease severity; however, we found a higher prevalence of amyloidosis development in patients with the M694V mutation. Five patients with amyloidosis had M694V heterozygosity (23.53%); M694V homozygosity was detected only in 3 (17.65 %) of them. E148Q heterozygosity was found only in 1 (5.8%) patient with amyloidosis. In addition, we found 8 patients without the mutation. We concluded that non-identification of mutations in these patients may be due to many factors, including the presence of other rare mutations, unknown mutations, or genetic heterogeneity and also some mutations that were not found in our strip assay. Consequently, the most common mutation was M694V, with 3 homozygous and 5 heterozygous forms. In conclusion, the most common mutation form was M694V heterozygosity (20.8%).

Colchicine treatment was used in some patients. Forty-one (32.8%) of 125 patients used only colchicine, and their response to the treatment was complete. Ten (8%) did not respond to colchicine treatment. Seventy-four also exhibited an incomplete response to colchicine and used a supportive treatment with the colchicine therapy for a significant effect. As a result, there was no significant difference in response to colchicine treatment between patients with various mutational distributions.

Clinical features varied in different populations. Fever was the most common symptom, occurring in about

93% to 100% of Turks, Arabs, Jews, and Armenians.[3] Although in some studies, arthritis was reported as a common symptom, followed by fever and abdominal pain. In 2009, Inal and colleagues[2] reported that fever was the most common symptom, and it was followed by abdominal pain or peritonitis.[4,26] In our study group, the most common symptoms were abdominal pain (79.1%) and fever (51.6%), which is similar to the findings by Inal and colleagues.[2] Arthritis was observed in 30.9% of patients. Diarrhea (6.7%, 30/446), vomiting (7.6%, 34/446), and constipation (3.6%, 16/446) were the other symptoms. Kone Paut et al reported diarrhea in 4% of the patients in their study group; nevertheless, our rate was higher than in their report.[27] Clinical manifestations were different between the different mutation profiles. In **Table 6**, mutational profiles and application criteria of patients are compared.

Sayarlioglu and colleagues[28] reported that only 14% (57/401) of patients had adult-onset FMF (disease onset at age over 20 years), and only 5 (1.3%) had the first attack after 40 years of age (late-onset FMF). Our study group consisted of patients with a large age range, and 68% (305/446) of our patients had ages in the range 0-20 years at the onset of FMF, 23.7% (106/446) had the adult-onset (21-40 years) FMF, and 7.8% had the late-onset (41-80) FMF. There might be some clinical and molecular differences in the onset of the disease.

Our study group included heterozygous (46.6%) and compound heterozygous (33.49%) mutations with the clinical manifestations of FMF disease. To date, it has been pointed out that FMF is an autoinflammatory disorder generally caused by recessively inherited mutations in the *MEFV* gene. FMF is quite prevalent in the Armenian population, in which majority of the patients have two mutated alleles; yet in 18% of symptomatic patients, just 1 mutation has been detected. To explain this finding, in 2010, Moradian and colleagues analyzed the symptoms and genotypes of 1299 patients, including 236 affected heterozygous patients with a definite diagnosis of FMF. They selected a subset of 63 heterozygous, homozygous, and asymptomatic normal individuals and completely sequenced their *MEFV* genes (exons) to discover any other mutations potentially missed by currently used screening methods. Besides four synonymous polymorphisms in exons 2 and 5, they found a T267I mutation in 1 heterozygous patient with a severe case of FMF who should have been designated as a compound heterozygote; yet the other genotypes were all accurate. They used a binomial probability distribution of symptoms in homozygous FMF patients to estimate the likelihood of their occurrences in heterozygous patients and demonstrated the assemblage of patients into groups with similar clinical criteria using statistical clustering. They found extremely high probabilities for the presence of FMF symptoms in heterozygous individuals and determined that symptoms were equally likely to occur in both genotypes analyzed. Therefore, their study supports the rising evidence that a single *MEFV* mutation could be associated with mild FMF symptoms. However, heterozygous patients presenting with a severe phenotype should be further analyzed for the less common second *MEFV* mutation using gene sequencing.[29]

Table 6. Mutation profiles and application criteria reported to the clinics.

	Number of patients (n)		
Mutation profile	**Fever**	**Abdominal pain**	**Arthritis**
Normal	100	172	50
Mutation group	130	181	88
Mutational distribution of the application criteria			
M694V heterozygote	23	34	20
M694V homozygote	15	20	16
E148Q heterozygote	14	20	9
E148Q homozygote	4	7	3
M680 (G/C) homozygote	12	14	7
M680 (G/C) heterozygote	7	12	5
Compound heterozygote	55	74	28

P=.04

This study established the spectrum of the *MEFV* mutations among Turk FMF patients. There seems to be a distinctive clinical picture, specifically a lower frequency of amyloidosis. The range and distribution of *MEFV* mutations in Turk patients are similar to those noted in other ethnic groups (M694V) often affected by FMF. However, the proportion of unidentified disease-causing *MEFV* mutations is higher in Turk patients. There is a need for further investigations for finding new etiologic factors or new undefined molecular techniques to identify new parameters. In conclusion, because of the genetic heterogeneity in Anatolia, larger serial country-based analyses are required to investigate the rate of these mutations, the association between the mutations on one hand and a family history of consanguinity and clinical manifestations on the other hand. Also, the high incidence of *MEFV* gene mutations in the Turkish population indicates that newborn screening may be required in the future.

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original article

Association of interleukin 4 (-590 T/C) and interleukin 4 receptor (Q551R A/G) gene polymorphisms with acne vulgaris

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BACKGROUND AND OBJECTIVES: Acne vulgaris is a common skin disorder. The complete etiology of this disease remains to be identified; however, it seems that aberrant expression of cytokine genes might be a contributing factor. This study aimed to investigate the association of genetic polymorphisms related to interleukin 4 (IL-4) promotor and receptor (IL-4R) genes as inflammatory modulators with acne vulgaris.
DESIGN AND SETTING: A case-control study 95 acne patients recruited from outpatient dermatology clinics affiliated with Qassim University, Qassim, Saudi Arabia.
PATIENTS AND METHODS: Acne patient data were compared with 87 normal healthy unrelated controls from the same locality. The genomic DNA was extracted and processed using the real-time polymerase chain reaction amplification for characterization of polymorphisms related to IL-4 (-590 T/C) and IL-4R (Q551R A/G) genes.
RESULTS: Acne patients compared to controls showed no significant difference in the frequencies of IL-4 (-590 T/C) polymorphic genotypes (P=.8), yet had a highly significant difference in IL-4R (Q551R A/G) genotypes (P<.001). The frequencies of the mutant genotype IL-4R GG as well as the allele IL-4R G were significantly higher in cases of acne than in controls. Furthermore, acne cases showed higher frequencies of combined genotypes IL-4R_GG with IL-4_CC, CT, or TT. However, no significant difference was noted on comparing subgroups related to disease severity or response to treatment (P>.05).
CONCLUSIONS: This study provides evidence for a significant association of IL-4R (Q551R A/G) genetic polymorphisms with the susceptibility rather than the severity of acne vulgaris.

Acne vulgaris is a relatively common skin disorder for which millions of patients seek dermatological care. It often leads to significant psychologic and physical morbidity. The pathogenesis is multifactorial and so far incompletely understood, taking into consideration that inflammation is a key component in its pathogenesis.[1-3] Although many cytokines have been implicated in the development and persistence of inflammatory immune responses, it is unknown if any of these are important in inflammatory acne. There has previously been some evidence that acne is a genetically determined disease, and could be inherited.[4,5] The detailed mode of inheritance remains unproven; however, it is most likely by a polygenic interaction mechanism with bacterial infection, like *Propionibacterium acne*, and with other products of inflammation probably under certain environmental conditions.[6] Candidate genes have been studied as those of human cytochrome P450 1A1, steroid 21-hydroxylase, epithelial mucin, androgen receptor, tumor necrosis factor alpha, tumor necrosis factor receptor 2, toll-like receptor 2, and CYP17.[7-14]

Interleukin 4 (IL-4) was originally discovered as a low molecular weight T cell–derived polypeptide of 129 amino acids, which is encoded by the IL-4 gene on chromosome 5q23.31. It is critical for immunoglobulin G subclass 1 (lgGl) production from mitogen-activated B cells. It is secreted by CD4 T cells, helper T cells type 2 (TH2) lymphocytes, and natural killer T cells, and by cells of the innate immune system, including mast cells, basophils, and eosinophils.[15-19] Now, it is clear that IL-4 regulates proliferation, apoptosis, gene expression, and differentiation in many hematopoietic cells; in particular, it directs the Ig class switch to IgG1 and IgE, and down-regulates the production of THl cells.[18,20-25]

The receptor for IL-4 is encoded by the interleukin 4 receptor (IL-4R) gene on chromosome 16p12. The human *IL-4R* gene spans about 51 kb and includes 12 exons.[26] The protein product of the membrane-bound form of IL-4R contains a signal peptide (exon 3), an extracellular domain (exons 3-7), a transmembrane domain (exon 9), and an intracellular domain (exons 10-12). Previously, 14 single nucleotide polymorphisms (SNPs) were identified in the coding region of the *IL-4R* gene.[27-30] Among the 8 replacement polymorphisms, 1 intracellular polymorphism (Gln551Arg) was proven to affect cell signaling in in vitro assays.[28,29,31] Several studies showed the variations in the *IL-4R* gene that have been associated with different diseases. IL-4R is a component of not only the IL-4, but also the IL-13 receptor and is essential for both the IL-4 and IL-13 signaling.

The type 1 IL-4 receptor is composed of two subunits, an α subunit (IL-4Rα), which binds IL-4 and transduces its growth-promoting and transcription-activating functions, and a γ c subunit, common to several cytokine receptors, that amplifies signaling of IL-4Rα.[32] IL-4 and IL-13 are cytokines that share immunoregulatory functions and a common IL-4RA chain on their receptors. They both play a central role in allergy by inducing IgE synthesis and both can inhibit inflammatory cytokines.[33,34] Interestingly, IL-4 and IL-13 showed a strong antitumor activity in mice; and, induced inhibition of proliferation of tumor cell lines.[35,36] Genetic alterations in the IL-13/IL-4R signaling pathway regulate TH1 or TH2 cytokine-driven inflammatory mechanisms.[37] Ueta et al suggested that IL-4R might be linked to innate immunity that constitutes a link between the environment and the adaptive immune system.[38] Hence, the speculation is that it affects immunological processes and disease susceptibility.[39]

The aim of this study was to investigate the association of SNP in the regulatory region (promoter) of IL-4 (-590 T/C), and with the receptor IL-4R (Q551R A/G) genes, in acne patients with the susceptibility and severity of disease in acne cases.

PATIENTS AND METHODS

This was a case-control study involving acne vulgaris patients (n=96, male=60, female=12, with a mean standard deviation [SD] age of 20.4 [3.5] years). They were recruited from the outpatient dermatology clinics affiliated with Qassim University. Acne vulgaris was unambiguously diagnosed by a consultant dermatologist. On the basis of severity of acne, patients were divided into three subgroups: mild, patients who exhibited mild-inflammatory acne; moderate, patients with inflammatory acne (acne papulopustulosa); and severe, patients with severe forms like the nodulocystic acne. Furthermore, the cases were also subgrouped as follows on the basis of response to treatment: with no response, with moderate response, or excellent response. Results obtained from the study subjects were compared with a control group of healthy unrelated subjects from the same locality (n=87, male=77, female=10, mean [SD] age: 20.1 [3.3] years). Conventional treatment was in the form of topical anti-acne agents including tretinoin creams and benzyl peroxide 5% in addition to systemic doxycycline. Patients were seen biweekly to evaluate the response and side effects of medications. To determine the efficacy of treatment on acne severity, we used both the total lesion count, which was calculated as papules + pustules + comedones + nodules, and the acne severity index, which was calculated as papules + (2 × pustules) + (comedones/4). Informed consent was obtained from all participants in addition to an ethical approval from the scientific and ethical committees of Qassim University. Peripheral blood samples were collected from all participants.

The isolation of DNA was done on a MagNA Pure LC instrument (Roche Molecular Biochemicals, Mannheim, Germany) using an LC DNA Isolation Kit LV (standard protocol; Roche Molecular Biochemicals). The LightCycler capillaries (Roche Diagnostics, Germany) and the reaction vessels, including the master mix, were placed into the postelution area. As soon as the postelution protocol started, the MagNA Pure LC automatically pipetted out 15 μL of the master mix and 5 μL of the processed sample into each of the LightCycler capillaries. Oligonucleotide primers and fluorescence-labeled hybridization probes were designed for amplification and sequence-specific detection of both IL-4 and IL-4R gene polymorphism. The primers and probes were obtained from TIB MolBiol (Berlin, Germany) as a premade lightmix standardized SNiP kit. The master mixture contained 2 μL of a 10 × mixture of LightCycler FastStart DNA master hybridization probes (Tib Mol Bol, Berlin, Germany), 5mM magnesium chloride ($MgCl_2$) (final concentration), 1μM final concentration of IL-4 and IL-4R-a primers, 0.075 μM final concentration of specific primers, and 0.2 μM final concentration of hybridization probes. The polymerase chain reaction (PCR) amplification and detection of the polymorphisms related to IL-4 (-590 T/C) (rs2243250) at the IL4 promoter region and the IL-4R (Q551R A/G) (rs1801275) at

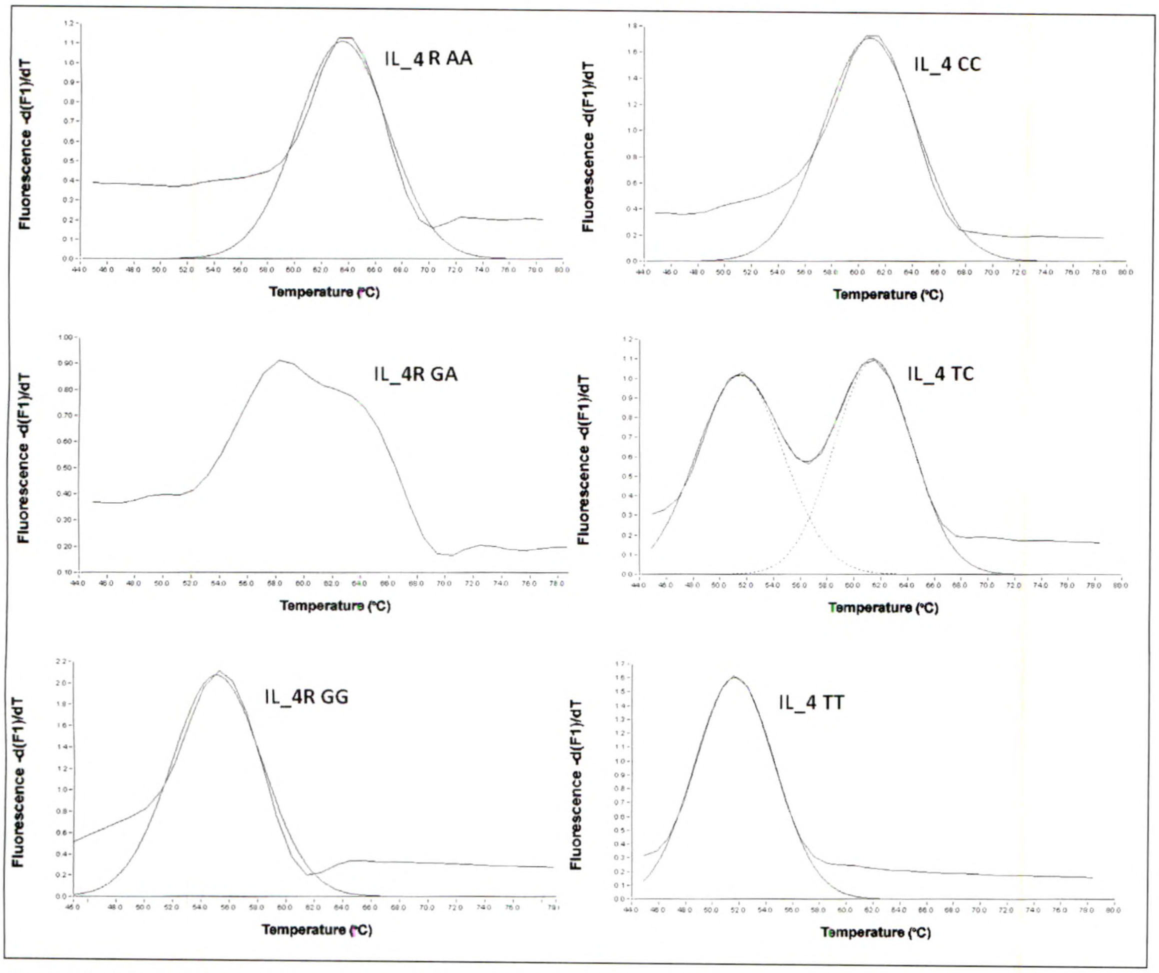

Figure 1. Real time polymerase chain reaction (RT PCR) tracing showing the melting curves corresponding to genetic polymorphisms of interleukin 4 [IL-4 (-590 T/C)] and interleukin 4 receptor [IL-4R (Q551R A/G)] genes.

the IL4 receptor gene using real-time PCR was done using LightCycler instrument (Roche Diagnostics, Mannheim, Germany). Fluorescence curves were analyzed at wavelengths of 640 and 705 nm (dual-color option). Each run contained a positive control for the wild type, and mutant and heterozygous standards in addition to a negative control of blank reagent and water. Each result was confirmed by the specific peak in the corresponding melting curve (**Figure 1**).

The statistical analysis was performed using the statistical software program Statistical Package for the Social Sciences (SPSS) version 13 (IBM Corp, Armonk, NY, United States). Comparisons between cases, control genotype, and allele frequencies were done using the chi-square test considering a *P* level of <.05 to be significant. In addition, the difference between the observed to that of the expected genotypes was tested using the Hardy Weinberg law of genetic equilibrium, and confirmed to be nonsignificant (*P*>.05).

RESULTS

When acne patients were compared with controls (**Table 1**) for the IL-4 (-590 T/C) genotype polymorphism, nonsignificant differences were noted with nearly equal frequencies i (TT vs TC-CC, *P*=.77). However, cases showed a significantly higher frequency of the IL-4R (Q551R A/G) homozygous mutant polymorphism GG than in controls (42.7% vs 8%, respectively) with a lower frequency of the wild type genotype AA in cases than in controls (55.2% vs 63.2%, respectively, *P*= <.001). The odds ratio (95% CI) of the frequency of GG genotype vs the GA and AA genotypes in cases compared to controls was 8.5 (3.6-20.4), which is relatively high. The allele frequency assessment confirmed the significant higher frequency of the IL-4R G allele (43.8% vs 22.4%) and lower frequency of the A allele (56.2 % vs 72.6%) in patients compared with controls (P<.001), with no significant difference related to the IL-4 allele frequencies (*P*>.05; **Table 2**). The odds ratio

Table 1. Genotypes related to interleukin 4 [IL-4 (-590 T/C)] and interleukin 4 receptor (IL-4R) (Q551R A/G) polymorphisms among cases compared to controls.

	Case n (%)	Control n (%)	χ^2	*P*
IL-4 (-590 T/C)				
CC	56 (58.9)	50 (53.8)		
CT	30 (31.6)	33 (35.5)	0.514	.773
TT	9 (9.5)	10 (10.8)		
IL-4R (Q551R A/G)				
GG	41 (42.7)	7 (8.0)		
GA	2 (2.1)	25 (28.7)	43.375	<.001
AA	53 (55.2)	55 (63.2)		

L-4. Interleukin 4; IL-4R. interleukin 4 receptor.

Table 2. Allele frequencies related to IL-4 (-590 T/C) and IL-4R (Q551R A/G) polymorphisms among cases compared to controls.

	Cases n (%)	Controls n (%)	χ^2	*P*
IL-4 (-590 T/C)	n=190	n=186		
C	142 (74.7)	133 (71.5)	0.5	.5
T	48 (25.3)	53 (28.5)		
IL-4R (Q551R A/G)	n=192	n=174		
G	84 (43.8)	39 (22.4)	18.6	<.001
A	108 (56.2)	135 (72.6)		

IL-4. Interleukin 4; IL-4R. interleukin 4 receptor.

Table 3. Genotypes related to IL-4 (-590 T/C) and IL-4R (Q551R A/G) polymorphisms among case-subgroups as regard severity of acne.

	Severity of acne			χ^2	*P*
	Mild n (%)	Moderate n (%)	Severe n (%)		
IL-4 (-590 T/C)					
CC	19 (57.6)	29 (58.0)	8 (66.7)		
CT	8 (24.2)	19 (38.0)	3 (25.0)	5.758	.22
TT	6 (18.2)	2 (4.0)	1 (8.3)		
IL-4R (Q551R A/G)					
GG	14 (41.2)	23 (46.0)	4 (33.3)		
GA	2 (5.9)	0 (.0)	0 (.0)	4.370	.40
AA	18 (52.9)	27 (54.0)	8 (66.7)		

IL-4. Interleukin 4; IL-4R. interleukin 4 receptor.

Table 4. Genotypes related to IL-4 and IL-4R polymorphisms among case-subgroups as regard response to treatment of acne.

	Response to treatment			χ^2	*P*
	No N (%)	Moderate N (%)	Excellent N (%)		
IL-4 (-590 T/C)					
CC	46 (59.0)	9 (64.3)	1 (33.3)		
CT	25 (32.1)	3 (21.4)	2 (66.7)	2.680	.613
TT	7 (9.0)	2 (14.3)	0 (.0)		
IL-4R (Q551R A/G)					
GG	32 (40.5)	6 (42.9)	3 (100.0)		
GA	2 (2.5)	0 (.0)	0 (.0)	4.536	.338
AA	45 (57.0)	8 (57.1)	0 (.0)		

IL-4. Interleukin 4; IL-4R. interleukin 4 receptor.

(95% confidence interval) of the frequency of the G allele vs the A allele in cases compared to controls was 2.7 (1.7-4.2). When compared case subgroups with different disease severity (**Table 3**) and response to treatment (**Table 4**) regarding the genotype frequencies of their IL-4 (-590 T/C) and IL-4R (Q551R A/G) polymorphisms, insignificant difference (*P*>.05) were observed.

The analysis of combined genotypes related to IL-4 (-590 T/C) and IL-4R (Q551R A/G) polymorphisms among cases and controls (**Table 5**) showed a significant increase in the frequency of CC + GG, TT + GG, and CT + GG genotypes in acne cases (21.1%, 3.2%, and 17.9%, respectively) compared to controls (4.6%, 0.0%, and 3.4%, respectively) with a decrease in the frequencies of the genotypes CC + GA, CT + GA, TT + GA, and CT + AA among cases (1.1%, 0.0%, 1.1%, and 13.7%, respectively) compared to controls (16.1%, 9.2%, 3.4%, and 20.7%, respectively, *P*=<.001).

DISCUSSION

Despite the power of modern approaches and persisting investigative efforts in the field of genetic association polymorphisms, acne vulgaris remains an enigmatic disorder so that the agent(s) triggering this disorder remain(s) to be identified.[8-15] In this work, the contribution of inflammatory component of acne imposed by the TH2 type cytokines is investigated through testing its association with IL-4 and IL-4R gene polymorphisms. To our knowledge, this is the first study searching in that direction taking into consideration the complex mechanisms interacting in the evolution of acne as a skin disorder.

Although the IL-4 (-590 T/C) polymorphism has been proven to affect the rate of transcription of IL-4 gene,[40] the present study showed no significant difference between cases and controls. Similarly, also no significant difference was observed in the frequency of IL-4 (-590 T/C) polymorphisms between cases and subgroups in terms of disease severity or treatment response. These results are similar to those described in a previous case-control study showing no effect of the mutant genotype IL-4 (-590) TT in a number of inflammatory diseases including multiple sclerosis in Iranian patients.[41] This finding probably indicates that the mechanism involved in the pathogenesis of acne is not controlled in particular by the IL-4 cytokine, but rather by other interactive genetic susceptibility factors.[8,10,12,42,43]

Interestingly, and in contrast to the aforementioned finding, this study showed an extremely significant difference between acne cases and controls in the distribution of polymorphic genotypes related to IL-4 receptor Gln551Arg gene. Acne cases showed a high significant increase in the mutant genotype with a high frequency of the mutant G allele, although there was also no significant difference in these genotypes between the acne cases subgroups related to disease severity or therapeutic response. In fact the A>G polymorphism of the *IL-4R* gene was reported to be involved in the enhancement of atopic and allergic conditions or other immune-mediated disorders through modified TH1- or TH2-driven inflammatory reactions[37] in addition to a probable role in the innate immunity of the skin.[38] In this respect, observing this extreme significant difference led us to speculate that the signaling of TH1 or TH2 inflammatory pathways may be also playing a role in acne pathogenesis through the control of IL-4 receptors and may represent a specific factor in the susceptibility of acne affliction. This is demonstrated more by the high frequencies of IL-4R GG genotype with all polymorphic genotypes of IL-4 (CC, CT, and TT). A further study is probably needed for estimation of cytokines, both in the serum and in the local acne lesions, and also culturing of skin cells may be required to learn whether TH1 and/or TH2 have a specific role in the pathogenesis of acne. We also recommend another wider scale study with more cases and controls to investigate all genetic and protein polymorphisms related to the TH2 inflammatory pathway. In conclusion, this study provides evidence for a significant association of IL-4 receptor Q551R (A/G) genetic polymorphism with the susceptibility, rather than the severity of acne vulgaris in affected subjects.

Table 5. Combined genotypes related to interleukin 4 [IL-4 (-590 T/C)] and interleukin 4 receptor [IL-4R (Q551R A/G)] polymorphisms among cases compared to controls.

IL-4/IL-4R	Case n=95 (%)	Control n=87 (%)	χ^2	P
CC/GG	20 (21.1)	4 (4.6)	44.61	<.001
CC/GA	1 (1.1)	14 (16.1)		
CC/AA	35 (36.8)	31 (35.6)		
CT/GG	17 (17.9)	3 (3.4)		
CT/GA	0 (.0)	8 (9.2)		
CT/AA	13 (13.7)	18 (20.7)		
TT/GG	3 (3.2)	0 (.0)		
TT/GA	1 (1.1)	3 (3.4)		
TT/AA	5 (5.3)	6 (6.9)		

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De novo malignancies after liver transplantation: a single-center experience

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BACKGROUND AND OBJECTIVES: The recipients of liver transplantation (LT) are subjected to lifelong immunosuppression with its many drawbacks. De novo and recurrent malignancy in transplant recipients are attributed to attenuation of immunosurveillance. In the present study, we present our experience with de novo malignancies encountered after both deceased and living donor liver transplantations.

DESIGN AND SETTING: Retrospective study of patients referred to LT center between April 2001 and January 2010.

PATIENTS AND METHODS: Various data were collected including type of malignancy and histopathologic features, immunosuppression regimen, and patient survival.

RESULTS: Of 248 LT procedures performed in 238 patients (10 retransplants), 8 patients (3.4%) developed de novo post-LT malignancies. De novo malignancies included post-LT lymphoproliferative disorders (PTLD) in 5 patients who were all Epstein-Barr virus (EBV) positive, and who were treated successfully with anti-CD20 monoclonal antibody therapy, reduction of immunosuppression, and control of EBV activity; urinary bladder cancer in 1 patient who was treated with radical surgical resection and chemotherapy but died of bone and lung metastasis within 1 year of diagnosis; endometrial carcinoma in 1 patient who was treated with radical surgical resection; and Kaposi sarcoma in 1 patient who was successfully treated with surgical excision and reduction of immunosuppression.

CONCLUSION: EBV-associated PTLD is the most frequently encountered de novo malignancy after LT and is easily treatable by chemotherapy and reduction of immunosuppression.

Liver transplantation (LT) is a well-established procedure for patients with acute and chronic liver failure. Many centers achieve patient and graft survival rates exceeding 90% in 1 year. However, the recipients of LT are subjected to lifelong immunosuppression with its many drawbacks.[1] De novo and recurrent malignancy in transplant recipients are attributed to attenuation of immunosurveillance.[2]

In recent years, de novo malignancy following LT has been increasingly reported,[3-7] and is suggested as a major cause of mortality in this population.[8,9] In 1968, Starzl was the first to predict an increased incidence of de novo malignancies in immunosuppressed organ transplant recipients and confirmed it shortly thereafter.[10] Single-center reports[11,12] have shown increased incidences of certain types of post-transplantation de novo malignancies, principally those linked to a viral cause. Estimates of developing de novo malignancies range from 4.1% to 16%, depending on the type and demographics of the transplant population, length of follow-up, and the era in which transplantations were performed.[13]

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PATIENTS AND METHODS

A total of 238 patients underwent 248 LTs (169 deceased donor liver transplantation [DDLT] and 79 living donor liver transplantation [LDLT]) procedures (10 retransplants) during a 9-year period between April 2001 and January 2010. Collected data were reviewed for age at the time of diagnosis of malignancy, cause of liver disease, interval from LT to diagnosis of malignancy, type of malignancy and histopathologic

Table 1. Timing of presentation of malignancies after orthotopic liver transplantation.

Case number	Type of malignancy	Timing of presentation after transplantation (months)
1	De novo PTLD	19
2	De novo PTLD	64
3	De novo bladder cancer	63
4	De novo endometrial cancer	16
5	De novo Kaposi sarcoma	8
6	De novo PTLD	2
7	De novo PTLD	2
8	De novo PTLD	20

PTLD: Post-transplant lymphoproliferative disorder.

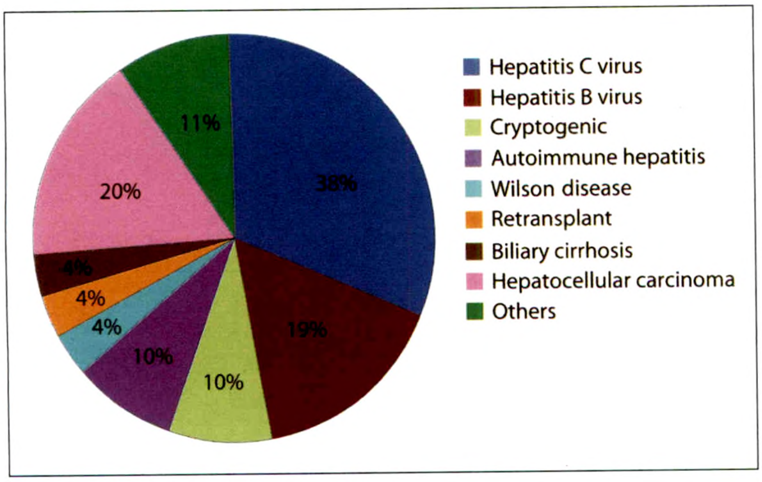

Figure 1. Indications for liver transplantation.

features, immunosuppression regimen, and patient survival. The primary immunosuppressive regimen was not significantly different among the cases and included a triple regimen of tacrolimus in combination with mycophenolate mofetil and prednisolone. The target blood level of tacrolimus was 8 to 10 µg/L immediately after surgery and aimed at 6 to 8 µg/L 6 months from transplantation. The dose of prednisolone was tapered to 5 mg daily 6 weeks post-transplant, and the withdrawal was achieved after 3 months. The diagnosis of de novo malignancy was confirmed by histology in all the cases. All the patients had undergone routine pretransplant tumor surveillance with chest radiography, mammography, and computed tomography within 1 year of transplant.

RESULTS

The overall male/female ratio was 152/96, the adult/pediatric ratio was 229/19, and the median age was 48 years (range 1.5-70). Over a 9-year period, 8 patients (3.4%) developed de novo post-LT malignancies at a median interval of 3.6 years from the time of LT and were identified through a search of a computerized hospital database. Among the study population were 5 men and 3 women. **Table 1** shows the type of de novo malignancy developed and its timing in relation to the LT. The episodes of rejection were not higher in patients who developed de novo malignancies. Immunosuppression was decreased in all the patients who were diagnosed with post-transplant lymphoproliferative disorders (PTLDs). Among the cases in the study population, chronic hepatitis C and hepatitis B were the leading causes of liver disease. Indications for LT are shown in **Figure 1**.

In the DDLT group, the median operating time was 7 hours (range 4-19), the median blood transfusion was 6 U (range 0-55), and the median hospital stay was 16 days (range 6-206). After a mean follow-up period of 2.7 years (range 1-9), the overall patient and graft survival rates were 81.5% and 79.7%, respectively.

In the LDLT group, the median operating time was 11 hours (range 7-17), the median blood transfusion was 6 U (range 0-65), and the median hospital stay was 16 days (range 7-266). After a mean follow-up period of 3.6 years (range 1-9), the overall patient and graft survival rates were 78.5% and 73.5%, respectively. Biliary complications were significantly higher in the LDLT group compared with the DDLT group at 34.2% vs 5.9%, respectively ($P<.05$). Vascular complications were significantly higher in LDLT group compared with the DDLT group at 13.9% vs 6.5%, respectively ($P<.05$).

De novo malignancies included PTLD in five patients who were all Epstein-Barr virus (EBV) positive; two pediatric patients presented with nasopharyngeal masses; and two adults presented with abdominal masses. One patient presented with upper gastrointestinal tract bleeding; the upper endoscopy showed a duodenal mass and the histopathology showed diffuse large B-cell lymphoma. All the five patients had B-cell type PTLD, and all of them were successfully treated with anti-CD20 monoclonal antibody therapy (rituximab), reduction of immunosuppression, and control of EBV activity. Urinary bladder cancer was diagnosed in 1 patient who was treated by radical surgical resection and chemotherapy, but unfortunately the patient died of bone and lung metastasis within 1 year of diagnosis. One patient developed endometrial carcinoma and was treated with radical surgical resection, but unfortunately died of aggressive tumor recurrence 1 year from the time of diagnosis. Kaposi sarcoma was diagnosed in one patient who was successfully treated with surgical excision and reduction of immunosuppression (**Figure 2**). A myeloproliferative disorder (MPD) was diagnosed in one patient who had LT for Budd-Chiari-related liver cirrhosis. This patient was being closely monitored for the possibility of developing acute leukemia post-transplant.

DISCUSSION

The reported incidence of de novo malignancies after LT has ranged from 4% to 16%, depending on the length of the follow-up, age distribution of the patients, and nature of the immunosuppressive regimen.[10] In this study involving 238 recipients of LT over a 9-year period, de novo malignancy was diagnosed in 8 patients (3.4%) at a median interval of 3.6 years from the time of LT. Herrero et al in 2005 reported after a median follow-up of 65 months the highest incidence of post-transplant malignancies at a rate of 26% (49 patients) in a cohort of 187 LT recipients.[14] Finkenstedt et al from Austria reported an incidence of 12.3% of de novo malignancies in a series of 779 consecutive LT recipients.[15] Moreover, Jain et al reported that in their large cohort of 1127 LT patients over a 10-year period, 6% developed de novo malignancies.[16] Only Saigal et al reported a lower incidence rate of 2.6%, but they did not include lymphoid tumors.[17] A plausible explanation for the discrepancies in the reported incidence rates includes the differences in the size of the population studies and the length of follow-up. The real incidence and factors increasing the risk are not completely defined. However, immunosuppression appears to be a major risk factor associated with the development of this serious complication.[3] Exogenous immunosuppression believed to be related to suppression of host defences (primarily T cells, which normally provide surveillance and protection from outgrowth of viral-infected cells).[10] This supports the finding that reduction or withdrawal of immunosuppression leads to regression of PTLD in many cases.[18] LT for alcohol-related liver disease was associated with a high probability of developing de novo cancers.[19] Interestingly, in our series, we had no LT for alcoholic liver disease because of the tradition of the study population. The lower incidence of post-transplant malignancies in the present study is not related to the length of the follow-up period as the median follow-up is 3.6 years, which is comparable to other studies.

In our series, PTLD was the most common type of post-transplant malignancy and all the patients were EBV positive, a finding that is consistent with the University of Pittsburgh experience.[10] These findings are in accordance with previous studies, which have shown that PTLD usually presents within the first or second year after LT.[20] We reported two pediatric patients in our series with PTLD. The Pittsburgh series included pediatric recipients, in whom the frequency of PTLD has been reported to be higher than adults.[21]

Figure 2. Kaposi sarcoma in the right leg which was successfully treated by surgical excision and reduction of immunosuppression.

The largest nonlymphoid class of de novo malignancies is skin cancer. The pathophysiological cause of skin cancer development is multifactorial, with sun exposure, race, age, and viral causes implicated.[10] Kaposi sarcoma is a viral-associated skin cancer, which is significantly higher in the transplantation population than in the general population.[22] The reported incidence of Kaposi sarcoma in the transplant population ranges from 0.18% to 6%. Marqués et al reported an incidence of 4% of Kaposi sarcoma in their large cohort of 528 patients undergoing LT with a mean follow-up of 2400 days.[23] In our study we had one patient diagnosed with Kaposi sarcoma who was successfully treated by surgical excision and reduction of immunosuppression.

Primary MPDs are a leading cause of Budd-Chiari syndrome, which frequently results in liver failure requiring LT. Acute leukemia occurred in 10% of patients with MPD.[24] There was a concern that immunosuppression after LT increased this risk.[25] The King's College group reported that of six patients with MPD, one patient developed acute leukemia after LT.[26] Dousset et al reported two patients with MPD and Budd-Chiari syndrome who had LT and developed leukemia (29 and 31 months) after LT.[27] In our series, we had one patient with MPD and Budd-Chiari syndrome; he had LT recently and has not developed acute leukemia in the short period of follow-up (8 months).

In conclusion, PTLD remains the most common de novo malignancy in post-LT patients. The increased incidence of de novo malignancies in LT recipients in comparison to the general population is because of known preexistent risk factors for cancer, greater rate of chronic viral infection, and long-term exogenous immunosuppression. This mandates careful long-term screening programs to help in early diagnosis of the disease.

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Intracranial germ cell tumors: a single-institution experience

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BACKGROUND AND OBJECTIVES: Intracranial germ cell tumors (GCTs) are not a common disease. We reviewed the experience of a single institution to determine the variables that affect treatment outcome.

DESIGN AND SETTING: A retrospective review of patients with the diagnosis of intracranial germ cell tumors treated in a single institution (KFSHRC) during the period from March 1985 to December 2007.

PATIENTS AND METHODS: Fifty-seven patients with the diagnosis of intracranial GCT were recorded in the KFSHRC Tumor Registry during the period from 1985 to 2007. Seven patients with a pineal region tumor treated as germinomas in the earlier years without a tissue diagnosis were excluded. This retrospective study was restricted to the remaining 50 patients with a tissue or marker diagnosis: 31 germinomas and 19 non-germinomatous germ cell tumors (NGGCTs).

RESULTS: The 10-year overall survival (OS), event-free survival (EFS) and relapse-free survival (RFS) were 87%, 88% and 96% for patients with germinoma, with a median follow-up of 4.5 (range 2-17) years, compared with 26%, 29% and 46% for patients with NGGCT with a median follow-up of 3 (range 1.5-13) years. For NGGCT, variables favorably influencing OS were younger age (< 16 y vs ≥16 y, *P*=.01), higher radiation dose (>50 Gy vs ≤50 Gy; *P*=.03) and later year of diagnosis (>1990 vs <1990 *P*=.002).

CONCLUSIONS: Tissue diagnosis of GCTs is mandatory prior to treatment except for patients with elevated markers. In germinoma, localized radiotherapy (RT) for M0 patients may be adequate. Long-term follow-up is needed to define the benefit of adding chemotherapy. For NGGCT, the use of combined modality treatment and RT dose >50 Gy are important factors that influence the outcome. Second-look surgery and resection of residual/refractory tumors is always recommended.

Primary intracranial germ-cell tumors (GCTs) are rare, accounting for 1% to 3% of all brain tumors in children.[1] Typically these are midline tumors arising from either the pineal or suprasellar region or occasionally both sites. They are more frequent in boys and have a peak incidence in puberty. These are rare tumors which encompass a multiple unique spectrum of tumor types, the management of which is dependent on the histological diagnosis.[2] The optimal management of intracranial GCTS remains to be established. During the last two decades, the principle treatment objective for germinomas has been to determine the minimum effective treatment that will maintain high tumor control rates. For non-germinomatous germ cell tumors (NGGCTs), the objective has been to improve survival rates by an appropriate combination, and as yet an intensification of systemic chemotherapy and radiation treatment.[3]

PATIENTS AND METHODS

King Faisal Specialist Hospital and Research Center (KFSHRC) provides general tertiary care services and includes the national cancer treatment center for Saudi Arabia. A total of 57 patients with intracranial GCTs were recorded in the Tumor Registry at the KFSHRC Cancer Center between 1985 and 2007. Seven patients treated for germinomas without a tissue diagnosis in the early years of the study were excluded. The medical files of the remaining 50 patients with GCTs were reviewed: 48 had a biopsy-proven diagnosis of intracranial GCTs, and two patients were diagnosed as having NGGCT based on imaging studies and elevated serum and cerebral spinal fluid. All patients underwent imaging of the brain; CT in earlier years of the study and MRI in the recent years. Staging workup included MRI of the spine (35 patients), CSF cytology (34 patients), and serum (50 patients) and CSF (20 patients) human chorionic gonadotrophins (HCG) and alpha-fetoprotein (AFP). There were 31 patients with germinomas, and 19 with NGGCT. Serum markers were elevated in 23 patients: 7/31 patients with germinoma had elevated HCG in the range of 25-100 mIU/mL. Among 19 NGGCT patients, elevated AFP was noted in nine patients, elevated HCG in one patient with choriocarcinoma, and elevated HCG as well as AFP in 4 patients. Overall, CSF cytology was positive in only 3 out of 34 (8%) patients with available data. In addition, there was MRI evidence of gross subarachnoid spinal disease (M3) in six patients.

The median age for the whole group was 12 (range 3-36) years. There were 39 males and 11 females. The tumor was located in the pineal region in 27 patients (54%), in the suprasellar region in 20 patients (40%), and 3 patients had multiple tumors arising in both regions (6%). The common presenting signs and symptoms were increased intracranial pressure (ICP) and hydrocephalus 54% (27 patients), visual impairment (acuity, diplopia, field deficits, blindness) 40% (20 patients), diabetes insipidus 22% (11 patients), endocrinopathies 30% (15 patients), Parinaud syndrome or other ocular palsy 10% (5 patients).

The database was analyzed using SPSS statistical software (IBM Corp. Armonk, NY, United States). The Kaplan-Meier method was used to calculate overall survival (OS), event-free survival (EFS) and relapse-free survival (RFS) curves, with 95% confidence intervals (CIs). Overall survival was defined from the date of diagnosis to the date of death or last follow-up. EFS was calculated from the date of diagnosis until the date of the first event, defined as relapse, progression, death from any cause, or last follow-up. RFS was calculated for patients who achieved a complete remission, from the date of diagnosis to the date of first relapse or of last follow-up. Univariate analyses were performed to evaluate variables influencing OS, such as age, gender, histology, radiation tumor dose, radiation volume, extent of surgery, use of chemotherapy, and year of diagnosis using the log rank test.

Overall, 48 patients underwent surgery: craniotomy and biopsy (27), partial resection (18) and total resection (3). For germinomas, craniospinal irradiation (CSRT) was used as a single-modality treatment in the early years of the study. Since 1992, the management guidelines for germinomas in the pediatric age group (<16 years) have changed from CSRT to elective bimodal therapy, use of upfront chemotherapy, with a reduction in the radiation volume and dose in order to reduce radiation toxicity. Three to four cycles of PVB (cisplatin+vinblastine+bleomycin) were followed by whole-brain RT plus boost with a 4 to 5 week gap between chemotherapy and RT. CSRT was only used in the high-risk group, defined as patients with metastatic disease, multiple tumor sites and/or elevated markers (HCG>100). The standard germinoma treatment for adults remained CSRT alone. CSRT was followed by a local boost with a 1-1.5-cm margin around the initial tumor. The RT dose to the whole brain was in the range 18-45 Gy (median, 30.6 Gy). The dose to the spine, when treated, was 18-37 Gy (median 32 Gy) and the dose to the primary tumor area was 30-55 Gy (median 48 Gy). Overall, 43 patients received RT: CSRT (24), whole brain and boost (11) and local RT alone (8). For NGGCT the intent was to use upfront chemotherapy and RT in all patients.

Germinoma patients (n=31)

The median age for the germinoma group was 12 (range, 3-36) years. There were 23 patients <16 years of age (22 were below the age of 14). There were 22 males and nine females. The tumor site was pineal in 16 (51%) and suprasellar in 12 (38%). Multiple midline germinomas were observed in three patients (11%): two patients presented with tumors in two sites (suprasellar and pineal regions), and one patient had diffuse tumor involving the suprasellar, thalamic/hypothalamic regions, the lateral and third ventricles.

The histology was consistent with pure germinoma in 26 patients, and germinoma with trophoblastic elements in 5 patients, in whom the serum HCG was elevated (<100 mIU/mL). The CSF cytology was positive in only 1 of 19 (5%) patients who had lumbar puncture (LP) studies.

A spinal MRI study was available in 23 patients, with gross evidence of subarachnoid spread (M3) in two patients. The extent of surgery was biopsy only in 17 (55%), partial resection in 12 (38%) and total resection in 2 (7%) patients. Adult patients were treated in the adult oncology unit with CSRT only, whereas 20/23 patients younger than the age of 16 years were treated according to the pediatric protocol in the pediatric oncology department. They received primary chemotherapy as part of their treatment. The chemotherapy regimen was PVB (cisplatin+etoposide+bleomyc) in

18 patients and PIV (cisplatin+ ifosfamide+etoposide) in two patients. The number of cycles ranged from one to seven, with most of the patients receiving three to four cycles (15 patients). This was followed by RT in 18 patients. There were two toxic deaths due to sepsis, after one and three cycles of chemotherapy. Overall, 28 patients with germinomas were treated with RT: CSRT plus boost (15), whole brain (WB) plus boost (11) and localized focal RT to tumor bed alone (2). Eight patients treated with CSRT also received chemotherapy.

NGGCT patients (n=19)

The median age was 14 (range, 4-35) years. There were 17 males and 2 females. The tumor site was pineal in 11 (58%), and suprasellar regions in 8 (42%) patients. The histology was mixed GCT in 5 patients (26%), malignant teratoma in 4 (21%), endodermal sinus tumor in 4 (21%), embryonal carcinoma in 2 (10%), choriocarcinoma in 2, and unspecified NGGCT in 2 patients. At the time of initial evaluation 12 patients had MRI spine and 14 had LP for CSF cytology. There was evidence of disease dissemination to the spine in 6 patients: gross positive spinal metastases on MRI (M3) in 4, and positive cytology (M1) in 2 patients. Seventeen of 19 (90%) patients had surgery: biopsy (10), partial resection (6), and total resection (1). Sixteen patients received chemotherapy as part of their initial combined modality therapy (CMT), and 3 patients were treated with CSRT alone in the early years of the study. The chemotherapy regimens included various combinations of cyclophosphamide, ifosfamide, vincristine, vinblastine, cisplatin, carboplatin, etoposide, bleomycin, VP16, methotrexate and prednisone. The use of platinum-based chemotherapy became a standard in our protocols in the year 1990. The chemotherapy regimens used were PVB (11 patients), PIV (4 patients), and MTX/CDDP/VP16 (1 patient). The number of cycles varied between two and six (median four cycles). Radiation treatment was given to 17/19 (90%) patients; CSRT (14 patients), whole brain (WB) plus boost (1 patient), and partial brain plus boost (2 patients). Two patients received no RT: one due to toxic death after three cycles of PVB, while the other died from disease progression after one cycle of PVB. The doses to the primary tumor volume were in the range of 45-55 Gy (median 50.4 Gy). The whole brain when treated, received 28-45 Gy (median 34.2 Gy). The dose to the spine varied between 24-37 Gy (median 34.6 Gy).

There were three toxic deaths secondary to chemotherapy. Twenty-six patients had documented endocrinopathies before initiation of treatment (panhypopituitarism, decreased growth hormone, growth retardation, hypothyroidism, hypogonadism, precocious puberty). An additional nine patients required hormone replacement therapy after completion of treatment, which may have been due in part to RT toxicity. Patients were not evaluated formally for neurocognitive deficits; however, difficulty in schooling, and lost grades were common among survivors. To date no second malignant tumors have been observed during follow-up of the survivors.

RESULTS

Germinoma patients (n=31)

The 10-year OS, EFS and RFS rates were 87%, 88% and 96% respectively (**Figures 1-3**), with a median follow-up of 4.5 years (range 3-17 years). A complete response (CR) was achieved in 30/31 patients. The response could not be evaluated in one patient who died from sepsis after the first cycle of chemotherapy. The other toxic death occurred in CR after three cycles of PEB, but prior to radiation treatment. There was only one death due to disease relapse. There was no significant OS and progression-free survival difference on univariate analysis by age, gender, site of disease, elevated HCG, extent of resection, the elective use of chemotherapy or the radiation volume or dose. In-field relapse after RT was not observed.

NGCCT patients (n=19)

The 10-year OS, EFS and RFS rates were 26%, 29% and 46% respectively (**Figures 1-3**). The median duration of follow-up was 3 (range 1-13) years. CR was achieved in 13/19 (68%) patients. Six patients (32%) developed progressive disease during initial chemo-

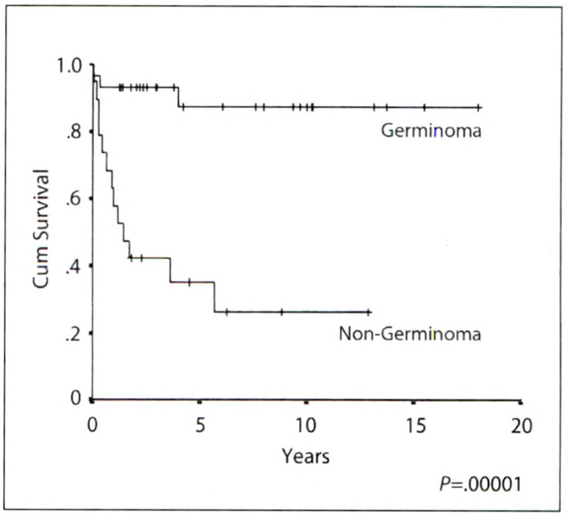

Figure 1. Overall survival.

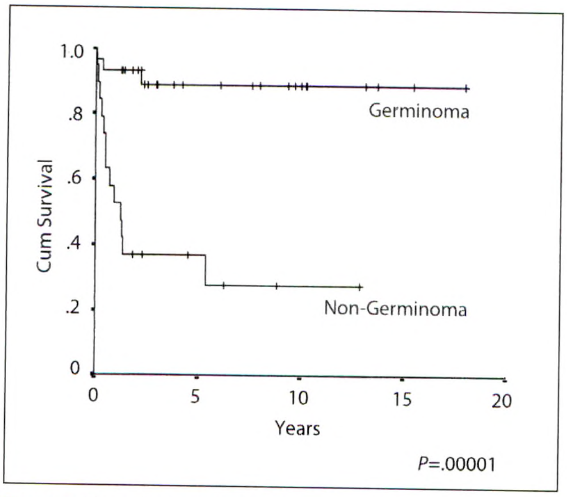

Figure 2. Event-free survival.

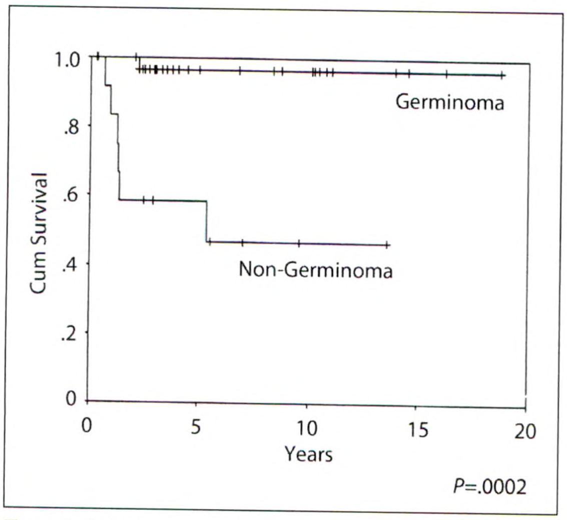

Figure 3. Relapse-free survival.

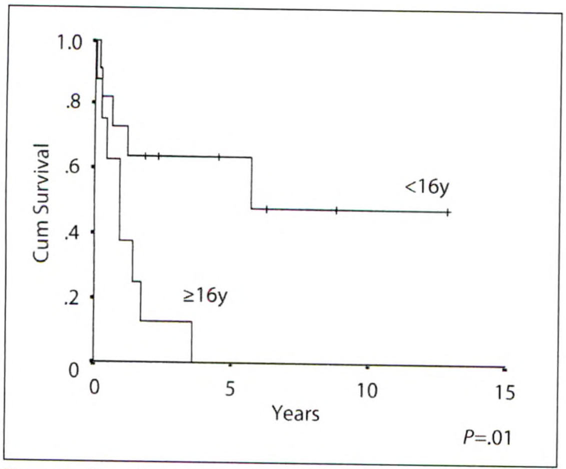

Figure 4. Overall survival and age in NGGCT.

therapy, and were excluded from the RFS analysis. The significant prognostic variables in univariate analysis were age, (OS 48% at 5 years for patients <16 years old and 0% ≥16 years, P=.01) (**Figure 4**), the time period of diagnosis, (OS at both 5 and 10 years was 45% for patients treated after 1990 and 0% for the period 1985-1990; P=.002) (**Figure 5**). For the radiation tumor dose, the five-year OS was 52% when the dose was ≥50 Gy (11 patients) compared with 17% when the dose was <50 Gy (6 patients) (P=.03) (**Figure 6**). In patients without spinal metastases at diagnosis, there were no significant differences in either local control or survival rates whether they were treated with CSRT, whole or partial brain RT.

Eleven patients died of disease, either from progression (PD) (5) or from relapse after an initial CR (6). The sites of relapse were local alone (3 patients), local plus spine (2 patients), local and extra-CNS metastases in one patient (liver and abdominal metastases). Five of the six patients with progressive disease died without achieving a remission.

DISCUSSION

Many important questions regarding the management of intracranial GCTs remain unanswered. The literature consists mainly of retrospective reviews and a small number of prospective single or multiple institution pilot studies.[4-6] Prospective randomized studies have not been practical because of the small number of cases. Most single-institution series have included patients without tissue diagnosis, and some have lumped together germinomas and all forms of NGGCT when reporting outcome, making it difficult to determine the optimal management.

For germinoma, CSRT is the standard treatment with an OS approaching 100%. The minimum effective dose and volume of radiation alone, in non-disseminated cases, remains undetermined. The influence of adding effective chemotherapy on these parameters is under investigation. A controversial issue is whether the spine needs to be irradiated when there is no evidence of dissemination. For localized germinomas, the standard of care has shifted from CSRT to localized RT with[4,7-9] or without chemotherapy.[10,11] The overall EFS rates appear to be the same for patients treated with RT or RT plus chemotherapy. CMT with neo-adjuvant chemotherapy has been explored with the objective of reducing radiation volumes and doses in young patients with limited disease (M0). Whereas there is an agreement upon the use of lower RT doses for subclinical disease with bimodal treatment (24-30 Gy CSRT, 40-45 Gy to the primary) in patients with disseminated disease,[12]

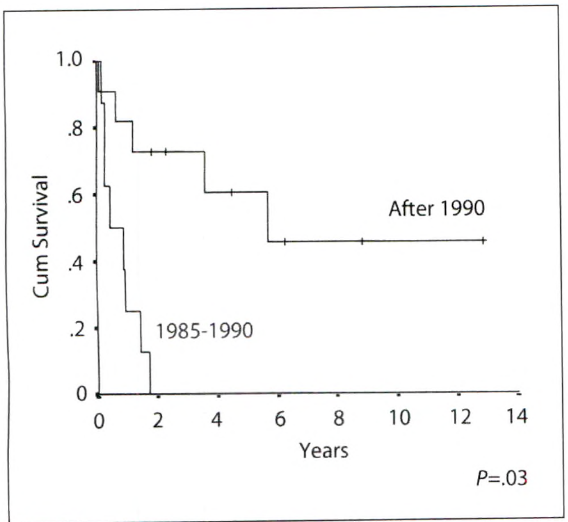

Figure 5. Overall survival by the time period of treatment.

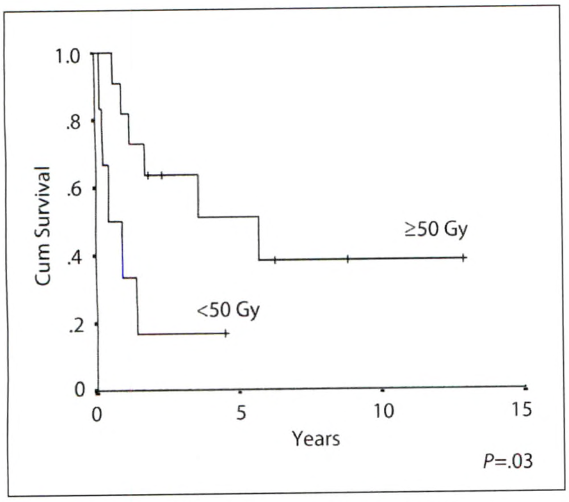

Figure 6. Overall survival and tumor dose in NGGCT.

controversies still exist regarding the definition of focal RT field volume for localized disease. For patients with limited disease, the initial RT volume varies from whole brain to partial brain or ventricular radiotherapy.[4,5] Conclusions are hard to draw, given the variations in patient selection and dose and volume for radiation given. In the SIOP, SFOP and MAKEI experiences, using chemotherapy with focal RT to tumor bed plus margin was associated with an excess relapse in the ventricular area of about 10% compared to the standard CSRT.[4-6] The spinal failure rates reported in the literature vary from 6%–36%.[4,5,13] On the other hand, a limited review that assessed five retrospective studies published after 1997, estimated an isolated spinal relapse rate of 9% in patients who received no spinal RT.[14] Two US studies that combined multicenter experiences in the treatment of intracranial GCT, concluded that CSRT is not indicated in the treatment of localized germinoma.[15]

The benefit of chemotherapy in germinomas is not yet proven; it is not clear whether with longer follow-up, CMT would substantially reduce late effects in comparison to CSRT, or whether CMT could be inferior because of the reduction in RT doses and volumes. Also, chemotherapy-related toxicity is not adequately reported in all studies. In a study from the Joint Center for Radiation Therapy, and Dana Farber Cancer Institute, Boston, that included 40 patients with the diagnosis of intracranial germinoma, the authors concluded that lower doses of CS-RT without chemotherapy appear to produce equally effective DFS and OS as do higher doses of RT or combination chemotherapy and RT.[10]

In a recent study from Japan, 165 patients with localized intracranial germinoma were treated with cranial RT without spinal irradiation. Fifteen patients (9.1%) developed spinal recurrences. In this study, large intracranial germinomas (>4 cm) and multifocal disease were independent risk factors for spinal relapse. Radiation field, RT dose and the use of chemotherapy did not affect the occurrence of spinal recurrences. Salvage treatment with chemotherapy and RT was effective in controlling the recurrent disease.[16]

Among the 31 patients with germinomas in our series, there was only one incidence of failure in a patient who was initially treated with chemotherapy followed by whole-brain RT. He developed isolated relapse in the spine, and died of disease progression despite salvage therapy.

In NGGCT, older reports on RT alone gave poor results with an OS of about 25%. Chemotherapy alone has been abandoned due to CNS progression and a relapse rate of 50%. Multimodality treatment integrating surgery, chemotherapy plus RT has become the standard over the last 25 years and has resulted in an OS increase to about 70%.[17,18] This survival improvement has been attributed to advances in diagnostic imaging and surgical technique, the use of platinum-based multi-agent chemotherapy, and CSRT. The Japanese group undertook a Phase II study to establish post-surgical combined chemotherapy and radiation therapy for primary intracranial GCTs, using different chemotherapy regimens for different prognostic groups based on histology.[19] Also, a collaborative effort led to the development of the International Germ Cell Cancer Collaborative Group (IGCCCG) risk criteria.[20]

Outcomes of NGGCTs depend on tumor type, hence the importance of establishing an accurate histological diagnosis.[21] This is often complicated by difficulties in obtaining adequate biopsy, and sampling errors in such heterogeneous tumors. Biopsy is mandatory except in patients where tumor markers are elevated at the time of presentation. While the desired extent of resection in germinomas is unclear,[22] total or subtotal resection, when practical with acceptable morbidity, was a common practice for NGGCT. The extent of initial surgical resection showed a prognostic significance in some series,[23] but not in others.[8] The introduction of highly effective cisplatin-based neoadjuvant chemotherapy obviated the need for upfront extensive resection in NGGCTs, since delayed resections have proven to be more complete and technically less difficult. In the SIOP 96 study, 40 patients with NGGCTs underwent surgery: 26 stereotactic procedures, 10 open biopsies and 33 attempted resections. There were 14 significant surgical complications, including three deaths. It was concluded that primary surgery was not beneficial for NGGCT patients.[18]

Recently, minimally invasive interventions such as endoscopic tumor biopsy (ETB) were introduced for establishing tissue diagnosis in pineal and third ventricle tumors.[24] These interventions have gained preference over open surgical techniques in many centers, since they seem to have lower complications and mortality than open craniotomy and sterotactic biopsy. It is not quite clear whether ETB is as accurate as stereotactic or open surgical biopsy. In a neurosurgical series from the UK, failure to provide an adequate endoscopic biopsy for accurate histological characterization has been reported in only 24% of the cases.[24]

There is scarce data addressing the appropriate RT field in NGGCT. Bimodal therapy with localized RT has been used for localized tumors. The question remains whether there are indications for CSRT other than tumor dissemination. In-field relapse or progression during RT is not uncommon, and RT doses >50 Gy are used. Salvage by second-line therapy is possible, but with a lower success rate than for germinoma.

In our series, except for one patient, local relapse in the primary site was a component of all failures. After chemotherapy for NGGCT of the brain or gonads, patients may continue to have residual radiologic abnormalities that may represent teratoma, necrosis, or residual GCT.[25] Teratoma is unresponsive to chemotherapy, and second surgical resection is the only effective treatment. This also applies to patients whose tumor markers have not normalized after initial chemotherapy, where second complete surgical resection may be more critical than recourse to more chemotherapy. This indicates the need for more aggressive local control primarily, whether in surgical approaches, and possibly higher RT doses in patients with residual disease. It also highlights the need for more intensive chemotherapy.

In the current series, the study time period showed to be a significant variable; there were no survivors among the eight patients with NGGCT treated between 1985-1989 as compared to a 45% five-year survival rate for patients treated after 1990 (11 patients). This could be attributed to improved anesthesia, neurosurgical and radiation therapy techniques, and better staging with the introduction of MRI at KFSHRC since 1990. Among the eight patients who were treated before 1990, none had MRI study of the spine. Some of these patients may have had disseminated disease that could have contributed to the poor outcome. The most important variable seems, however, to be the use of more aggressive platinum-based pediatric protocols, and better aggressive supportive treatment at our institution since 1990.

The superior OS in patients younger than 16 years of age (5-year OS 48% for <16 years old and 0% ≥16 years, $P=0.01$), is probably attributed to the use of more aggressive chemotherapy and supportive treatment pediatric protocols for this age group, as compared to the adult protocols used at our institution. In the early years of the study, three adult patients with NGGCT were treated with RT only without chemotherapy, which could be another contributing factor.

Tissue diagnosis of GCTs is mandatory prior to treatment except for patients with elevated markers. In germinoma, localized RT for M0 patients may be adequate. The determination of the RT volume and minimum effective dose remains to be determined. Long-term follow-up is needed to define the benefit of adding chemotherapy. For NGGCT, the use of CMT, and RT dose >50 Gy are important factors that influence outcome. The determination of which patients may be treated with local RT is the main question. Second-look surgery and resection of residual/ refractory tumors is always recommended.

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original article

Are acute coronary syndrome patients admitted during off-duty hours treated differently? An analysis of the Saudi Project for Assessment of Acute Coronary Syndrome (SPACE) study

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BACKGROUND AND OBJECTIVES: It is often suggested that acute coronary syndrome (ACS) patients admitted during off-duty hours (OH) have a worse clinical outcome than those admitted during regular working hours (RH). Our objective was to compare the management and hospital outcomes of ACS patients admitted during OH with those admitted during RH.

DESIGN AND SETTING: Prospective observational study of ACS patients enrolled in the Saudi Project for Assessment of Acute Coronary Syndrome study from December 2005 to December 2007.

PATIENTS AND METHODS: ACS patients with available date and admission times were included. RH were defined as weekdays, 8 AM-5 PM, and OH was defined as weekdays 5 PM-8 AM, weekends, during Eid (a period of several days marking the end of two major Islamic holidays), and national days.

RESULTS: Of the 2825 patients qualifying for this analysis, 1016 (36%) were admitted during RH and 1809 (64%) during OH. OH patients were more likely to present with heart failure and ST elevation myocardial infarction (STEMI) and to receive fibrinolytic therapy, but were less likely to undergo primary percutaneous coronary interventions (PCI). The median door to balloon time was significantly longer (*P*<.01) in OH patients (122 min) than in RH patients. No differences were observed in hospital outcomes including mortality between the two groups, except for higher heart failure rates in OH patients (11.1% vs 7.2%, *P*<.001).

CONCLUSIONS: STEMI patients admitted during OH were disadvantaged with respect to use and speed of delivery of primary PCI but not fibrinolytic therapy. Hospitals providing primary PCI during OH should aim to deliver it in a timely manner throughout the day.

A favorable clinical outcome in patients with acute coronary syndromes (ACS) depends on the timely delivery of proven therapies.[1-3] In patients with ST elevation myocardial infarction (STEMI), a short door to needle time (DNT) and a door to balloon time (DBT) are evidence-based quality indicators for optimal reperfusion associated with improved survival.[1,3,4] Hospitals provide routine care during regular working hours (RH), while only providing emergency care during off-duty hours (OH), weekends, and holidays.[5] Previous studies suggest that outcomes are worse in ACS patients presenting to the hospital during OH.[5,6] Such a disparity may be more pronounced in developing countries because of general shortages in health care professionals and poor health care service management.[7]

Despite tremendous improvement in cardiac care in Saudi Arabia, patterns of medical practice and hospital outcomes for ACS patients presenting during OH is still unknown. We sought to evaluate the potential inequality in management and in-hospital outcomes of patients enrolled in the Saudi Project for Assessment of Acute Coronary Syndrome (SPACE) who presented during RH and OH.

PATIENTS AND METHODS

The SPACE study was a prospective, multicenter, observational study of all consecutive acute coronary syndrome (ACS) patients admitted to participating hospitals from the start of December 2005 until the end of December 2007. A full description of the design was previously reported.[8] Seventeen hospitals from five regions of Saudi Arabia participated in the registry. Centers involved were from the following cities: Riyadh, Jeddah, Dammam, Buraidah, Tabuk, Khamis Mushayt, and Al Kharj. All participating hospitals were in urban areas. A total of 70% of these hospitals had cardiac catheterization laboratories, and 60% had on-site cardiac surgery backup. Only two centers had a primary percutaneous coronary interventions (PCI) programs for all STEMI comers; however other centers offered primary PCI sporadically. Where required, ethics approval was obtained from the institutional review board of individual hospitals. The diagnosis of STEMI, non-ST elevation myocardial infarction (NSTEMI), unstable angina, and other adverse endpoints analyzed in this study were based on the definitions of the Joint Committee of the European Society of Cardiology/American College of Cardiology, published in December 2001.[4] Patients with the diagnosis of NSTEMI and unstable angina were grouped in the category of non-ST elevation acute coronary syndrome (NSTEACS).

Data collection was performed using a standardized case report form. Collected data included patient demographics, past medical history, provisional diagnosis on admission and final discharge diagnosis, electrocardiographic findings, laboratory investigations, medical therapy, use of cardiac procedures and interventions, in-hospital outcomes, and overall mortality.

Study patients

Admission date and time information was required for all ACS patients enrolled in the SPACE registry to be included in this analysis. Patients referred from other hospitals were excluded, as their referral was mostly planned and details on their admission times in the referring hospital was not available. Patients were assigned to the RH group if they were admitted during regular duty hours between 8 AM and 5 PM. In the OH group were patients admitted between 5 PM and 8 AM, weekends defined as Wednesday 5 PM to Saturday 8 AM, religious holidays (two Eid holidays), and the national day holiday. This classification was mainly based on differences in staffing between the two time periods. Baseline characteristics, clinical presentations, and in-hospital therapies were compared between groups. Outcome measures included: in-hospital all-cause mortality, reinfarction, heart failure, cardiogenic shock stroke, and major bleeding.

Statistical analysis

Categorical data are presented as frequencies and percentages, and continuous data were summarized using means and SD or medians and interquartile ranges based on satisfying the normality assumption. Statistical comparisons between the RH and OH groups were carried out using chi-square test for categorical variables and independent *t* test or Mann-Whitney U test as appropriate for continuous variables. All analyses were performed using SPSS software (IBM Corp, Armonk, NY USA).

RESULTS

Of the 5055 ACS patients admitted to Saudi hospitals during the study period, 2230 were excluded as they were referred from other centers. Of the remaining patients only 2825 (55.9%) had details on admission times and were included in this study. The majority of patients (1809, 64%) were admitted during off hours, while 1016 (36%) were admitted during regular hours. **Table 1** reports baseline characteristics of both groups. The mean (SD) age of the study population was 57.7 (13.2) years; the population was predominately male and composed of Saudi nationals. Diabetes mellitus and hypertension were highly prevalent (56.8% and 56.3%, respectively). In addition, vascular disease in the form of coronary artery disease, peripheral arterial disease, and cerebrovascular disease were found in at least half of the study cohort.

Baseline characteristics and clinical presentation were similar between patients presenting in RH and those presenting in OH. Differences included a higher baseline creatinine and a lower rate of prior PCI in the OH group. OH patients were more likely to present with heart failure (24% vs 19.1%, P=.002), tachycardia (17.4% vs 10.1%, P<.001), and presented to the hospital earlier following symptom onset (105 min vs 137 min, P<.001). In addition, STEMI patients presented more often in OH than RH (762 [42.1%] vs 377 [37.1%], P=.009, respectively), while NSTACS patients pre-

Table 1. Baseline patient characteristics.

	Overall (N=2825)	Regular hours (n=1016)	Off hours (n=1809)	*P*
Age (mean, SD)	57.7 (13.2)	57.9 (13.2)	57.6 (13.3)	.573
Males (%)	2216 (78.4)	802 (28.9)	1414 (78.2)	.632
Saudi (%)	2197 (77.8)	797 (77.8)	1400 (77.4)	.518
Diabetes mellitus (%)	1603 (56.8)	584 (57.5)	1019 (56.4)	.566
Hypertension (%)	1591 (56.3)	571 (56.2)	1020 (56.4)	.870
Smoking (%)	953 (33.9)	324 (31.8)	629 (34.7)	.115
Dyslipidemia (%)	291 (25.9)	105 (28.2)	186 (24.7)	.456
Waist circumference (median, IQR)	98.0 (18)	99 (19)	98 (18)	.649
BMI (median, IQR)	27.7 (6.3)	27.7 (6.2)	27.7 (6.4)	.681
Symptom to admission time (median, min)	120 (173)	137 (190)	105 (165)	<.001
History of coronary artery disease (%)	482 (47.5)	797 (44.1)	1279 (45.3)	.075
Prior PCI (%)	456 (16.1)	179 (17.6)	277 (15.3)	.009
Prior CABG (%)	183 (6.5)	65 (6.4)	118 (6.5)	.092
History of PAD (%)	124 (4.4)	363 (3.5)	88 (4.9)	.277
History of CVA (%)	179 (6.3)	56 (5.5)	123 (6.8)	.092
Creatinine, μmol/dl (median, IQR)	92.0 (32)	90.0 (26)	92.0 (29)	.001
Hemoglobin g/dL (median, IQR)	14.0 (3)	14 (2)	14 (3)	.721
FBS, μmol/dL (median, IQR)	6.6 (4)	6.6 (4)	6.7 (4)	.516
HR >100 bpm (%)	417 (14.8)	103 (10.1)	314 (17.4)	<.001
SBP ≤90 mm Hg (%)	81 (2.9)	30 (3.0)	51 (2.8)	.631
Heart failure (%)	627 (22.3)	193 (19.1)	434 (24.0)	.002
STEMI <12 hr (%)[a]	927 (81.4)	309 (81.9)	618 (81.1)	.441
Anterior STEMI (%)[a]	623 (56.1)	221 (59.8)	402 (54.2)	.772
ECG to admission time, min (median, IQR)	14 (16.5)	10.0 (16.0)	10.0 (15.0)	.405
LVEF <35% (%)	881 (31.2)	306 (30.1)	575 (31.8)	.359
3V or LM coronary disease (%)	621 (22)	233 (22.9)	388 (21.4)	.360

BMI: Body mass index; IQR: interquartile ranges; SD: standard deviation; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; PAD: peripheral arterial disease; CVA: cerebrovascular accidents; HR: heart rate; SBP: systolic blood pressure; STEMI: ST elevation myocardial infarction; ECG: electrocardiography; LVEF: left ventricular ejection fraction; 3V: three vessel; LM: Left main.

[a] Proportions were out of the total STEMI patients.

Table 2. Hospital therapies.

	Overall (N=2825)	Regular hours (n=1016)	Off hours (n=1809)	*P*
Aspirin (%)	2775 (98.5)	991(97.9)	1784 (98.8)	.075
Clopidogrel (%)	2458 (87.3)	879 (86.9)	1579 (87.5)	.635
Beta-blockers (%)	2369 (84.1)	869 (85.9)	1500 (83.1)	.050
Statins (%)	2722 (96.6)	980 (96.8)	1742 (96.5)	.592
ACE I (%)	2002 (71.0)	727 (71.8)	1275 (70.6)	.486
ARB (%)	179 (6.4)	57 (5.6)	122 (6.8)	.238
Heparin (%)	2544 (90.1)	887 (87.5)	1657 (91.6)	<.001
GP 2b 3a inhibitors (%)	838 (29.7)	303 (29.9)	535 (29.6)	.864
Fibrinolytic use (%)[a]	653 (70.4)	199 (64.4)	454 (73.5)	.004
ECG to admission time, min (median, IQR)	14 (16.5)	10.0 (16.0)	10.0 (15.0)	.405
DNT (median, IQR)	54 (60)	50.0 (52.5)	54.5 (67.2)	.336
DNT <30min (%)[b]	94 (14.4)	26 (13.2)	68 (15.0)	.553
Fibrinolytic short fall (%)	208 (14.4)	81 (7.9)	127 (7)	.352
Primary PCI (%)[a]	158 (17)	66 (21.4)	92 (14.9)	.014
DBT Median, min (IQR)	110.5 (72.8)	96 (49)	122 (92)	.002
DBT <90 min (%)	46 (31.1)	24 (39.3)	22 (25.3)	.069
Hospital length of stay, days (median, IQR)	5 (5)	5 (5)	5 (5)	.802

ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; GP 2b 3a inhibitors: glycoprotein 2b 3a inhibitors; DNT: door to needle time; DBT: door to balloon time; Fibrinolytic short fall: eligible for fibrinolytic therapy but did not receive it; IQR: interquartile ranges; SD: standard deviation.

[a] Proportions were out of the STEMI patients presenting within 12 hours of chest pain onset; [b] Proportions were out of STEMI patients receiving fibrinolytic therapy.

Table 3. In-hospital outcomes.

Outcome	Overall (N=2825)	Regular hours (n=1016)	Off hours (n=1809)	*P*
Overall death (%)	92 (3.3)	32 (3.2)	60 (3.3)	.234
Death in STEMI	57 (5)	17 (4.5)	40 (5.2)	.590
Overall re-infarction	30 (1.1)	11 (1.1)	19 (1.1)	.935
Major bleeding	36 (1.3)	17 (1.7)	19 (1.1)	.157
Stroke/TIA	23 (0.8)	9 (0.9)	14 (0.8)	.751
Heart failure	273 (9.7)	73 (7.2)	200 (11.1)	<.001
Cardiogenic shock	125 (4.4)	35 (3.4)	90 (5.0)	.058

STEMI: ST elevation myocardial infarction; TIA: transient ischemic attacks.

sented more often during RH than OH (637 [62.8%] vs 1047 [57.8%]), $P<.001$, respectively). The predominant STEMI location was anterior (56.1%) (**Table 1**).

Hospital therapies

Distribution and frequencies of in-hospital therapies dispensed to patients were similar between groups with the exception of beta-blockers, heparin, and fibrinolytic agents (**Table 2**). Heparin and fibrinolytic agents were given more frequently and beta-blockers were given much less frequently to patients presenting during OH. No significant differences were observed between the two groups with regard to DNT or the proportion of patients meeting a DNT <30 min. Primary PCI was performed in only 17% of the study cohort; however it was performed less in STEMI patients presenting during OH. In addition, the DBT was significantly longer. A DBT ≤90 minutes was achieved in only 31.1% of the overall cohort, with a statistical trend toward a lower proportion of patients meeting this quality indicator if admitted during OH periods (**Table 2**).

In-hospital outcomes

Table 3 shows hospital outcomes of the two groups. No significant differences were observed in hospital outcomes except for significantly higher heart failure events in the OH group (11.1% vs 7.2%, $P<.001$). A marginal trend for a higher occurrence of cardiogenic shock was observed in OH patients compared to those admitted during RH.

DISCUSSION

The results of this analysis provide insights into "real world" management of ACS patients in Saudi Arabia according to the time and day of admission. We found that higher risk ACS presentations, namely, STEMI and heart failure, were seen more frequently during OH. These findings are concordant with some previous reports[6,9,10] but disagree with others.[11-13] Additionally, although PCI was not used frequently in this ACS cohort as a whole, primary PCI was used less in OH patients; when performed, significant delays in DBT were observed both in absolute time and in the proportion of patients achieving a target of less than 90 minutes. Only 2 hospitals out of the 17 participating hospitals offered primary PCI as a default reperfusion strategy for all STEMI comers. This explains to a large extent why this study included a small number of patients receiving primary PCI. Numerous reports showed similar delays in the performance of primary PCI.[6,10,12] Despite the higher risk profile of patients admitted during OH and delays in the performance of primary PCI in STEMI patients in OH patients, no difference in hospital outcomes was observed, except for a significantly higher heart failure rates and a trend toward more cardiogenic shock among patients presenting during OH. The higher in-hospital heart failure rate seen in OH patients is potentially due to the higher rate of heart failure on initial hospital presentation. Data on hospital outcomes in ACS patients admitted during off-hour periods is conflicting. Magid et al showed that patients presenting during OH had significantly higher adjusted in-hospital mortality than patients presenting during RH.[6] A similar finding was demonstrated using the Myocardial Infarction Data Acquisition System, which analyzed 231 164 AMI patients. Both short- and long-term mortality was higher in patients admitted on weekends compared to those admitted on weekdays.[5] On the other hand, our study confirmed the findings of numerous other reports that did not show any difference in adverse outcomes.[9-12] The more frequent administration of fibrinolytic agents in the OH group most likely stems from the fact that STEMI was the predominant presentation in that time period; however, it is unclear why heparin was utilized more frequently in the OH group. Although no differences in DNT were observed between the two groups, it must be stated that the absolute DNT in both groups was significantly longer than the standard DNT of less than 30 minutes. This is a significant care gap that needs to be narrowed by training and empowering emergency care physicians, the first responders to STEMI patients, to administer fibrinolytic agents in a timely manner.

An intriguing finding in this study was that the symptom onset to admission time was shorter in patients presenting during OH times. The reasons behind this observation are unclear; a possible explanation is that STEMI and heart failure, both seen more in OH patients, generally present with more severe symptoms than with NSTEACS patients, leading to a greater urgency in presenting to the emergency room. Another possible explanation is easier access to care during OH owing to less traffic or pressure on the emergency rooms in off hours, weekends, or holidays. Woman are not permitted by law to drive in Saudi Arabia. This may have been a potential factor in delays seen in hospital presentation, or presentation during OH when a male family member is available after work hours for transportation.

Our study suffers from several limitations. This is an observational study; therefore selection bias inherent in the study design could not be avoided. Although we found disparities in the utilization and rapidity of delivering primary PCI between the 2 groups, this did not seem to have an impact on hospital mortality; this might be because of the small sample size. In addition, data on post-discharge outcomes were not available, and we could not assess the impact of hospital therapeutic disparities on long-term outcomes. A considerable number of patients had missing admission times, which produces potential bias in either direction that might impact study results.

In conclusion, our findings suggest that ACS patients who presented during OH were likely to have a higher risk profile on admission but were generally treated equally to their counterparts presenting during regular hours, except for a lower utilization of primary PCI and longer delays in DBT when primary PCI was performed. Patients presenting in off hours suffered from higher rates of heart failure, but were no different with respect to other hospital outcomes compared to patients admitted during regular hours. These findings highlight existing disparities in health care services delivery in Saudi Arabia, and are potentially related to inadequate staffing and/or staff fatigue during off hours. Moreover, although primary PCI has been shown to be more efficacious in achieving reperfusion in STEMI patients, only a few centers offered it. Future research should address the root causes for such care gaps, and explore the clinical impact for implementing quality initiatives to improve these management shortfalls.

Acknowledgments and Conflict of Interest

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original article

Incidence of ventricular arrhythmia and associated patient outcomes in hospitalized acute coronary syndrome patients in Saudi Arabia: findings from the registry of the Saudi Project for Assessment of Acute Coronary Syndrome (SPACE)

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BACKGROUND AND OBJECTIVES: Mortality in acute coronary syndrome (ACS) patients with ventricular arrhythmia (VA) has been shown to be higher than those without VA. However, there is a paucity of data on VA among ACS patients in the Middle Eastern countries.

DESIGN AND SETTING: Prospective study of patients admitted in 17 government hospitals with ACS between December 2005 and December 2007.

PATIENTS AND METHODS: Patients were categorized as having VA if they experienced either ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) or both.

RESULTS: Of 5055 patients with ACS enrolled in the SPACE registry, 168 (3.3%) were diagnosed with VA and 151 (98.8%) occurred in-hospital. The vast majority (74.4%) occurred in patients with ST-segment elevation myocardial infarction. In addition, males were twice as likely to develop VA than females (OR 1.7; 95% CI 1.1-3). Killip class >I (OR 2.0; 95% CI 1.3-3.1); and systolic blood pressure <90 mm Hg (OR 6.4; 95% CI 3.5-11.8) were positively associated with VA. Those admitted with hyperlipidemia (OR 0.49; 95% CI 0.3-0.7) had a lower risk of developing VA. Adverse in-hospital outcomes including re-myocardial infarction, cardiogenic shock, congestive heart failure, major bleeding, and stroke were higher for patients with VA ($P \leq .01$ for all variables) and signified a poor prognosis. The in-hospital mortality rate was significantly higher in VA patients compared with non-VA patients (27% vs 2.2%; P=.001).

CONCLUSIONS: In-hospital VA in Saudi patients with ACS was associated with remarkably high rates of adverse events and increased in-hospital mortality. Using a well-developed registry data with a large number of patients, our study documented for the first time the prevalence and risk factors of VA in unselected population of ACS.

Acute coronary syndrome (ACS), including ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA), is a major life-threatening manifestation of coronary artery disease.[1-3] Moreover, data from early in the thrombolytic era indicate that STEMI complicated by ventricular arrhythmia (VA) is associated with a greater risk of short- and long-term mortality.[4-6] This increased mortality rate has been shown with VA following NSTEMI as well.[7] Data from the Global Registry of Acute Coronary Events (GRACE) Registry also showed a higher hospital mortality rate when VA complicated ACS and allowed identification of variables associated with the occurrence of VA.[8] The incidence and prognosis of VA in ACS are not yet reported from Saudi Arabia. Accordingly, data in the Saudi Project for Assessment of Coronary Events (SPACE) registry were accessed to describe the incidence of clinical outcomes associated with VA in patients hospitalized with ACS in Saudi Arabia. Patient characteristics associated with an increased risk for developing VA were examined to establish a baseline from which further studies can determine temporal changes in the magnitude and prognosis associated with VA-related ACS.

PATIENTS AND METHODS

This was a sub-study of the multicenter, prospective SPACE registry of ACS patients admitted to 17 government hospitals in Saudi Arabia between December 2005 and December 2007.[9] Patients were categorized as having VA if they experienced either ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) or both. VF was identified at admission or during the process of hospitalization if the patient showed irregular undulations of the electrocardiogram consistent with the diagnosis.[8] VT was identified by a regular wide complex tachycardia lasting >30 seconds or requiring termination because of hemodynamic instability.[8] VA could be identified on presentation or during the index hospitalization.

An assigned physician in each hospital acquired patient data that were entered by trained study coordinators onto standardized electronic case report forms (CRFs) throughout the hospital stay for each patient. Data included the following variables for which definitions were standardized among participating hospitals: patient demographics, medical history, presenting symptoms, provisional diagnosis on admission and final discharge diagnosis, biochemical and electrocardiographic findings, laboratory investigations, medical therapy, use of cardiac procedures and interventions, in-hospital outcomes, and in-hospital mortality. All cases were categorized as STEMI, NSTEMI, or UA using the definition proposed by the Joint Committee of the European Society of Cardiology/American College of Cardiology.[3] Cardiologists verified the completed CRFs and submitted them to the principal coordinating center where they were further checked for data quality, and queries were resolved before final analysis. All participating centers obtained ethics approval.

Differences in categorical variables between respective comparison groups were analyzed using the chi-square test or Fisher exact test. Continuous variables were analyzed using a *t* test or Mann-Whitney *U* test based on the satisfaction of normality assumption. *P* values are reported as 2-sided test results with a 5% level of significance for each test. Multiple logistic regression analysis was used to identify factors associated with VA. Variables considered for inclusion were baseline demographic characteristics (age, gender), medical history diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, angina, myocardial infarction [MI], cerebrovascular accident, percutaneous coronary intervention [PCI], coronary artery bypass graft), personal history (smoking), clinical presentation (Killip class >I, heart rate [HR], systolic blood pressure, ejection fraction), and discharge diagnosis (STEMI, NSTEMI, UA). Further, logistic regression models were used to assess the possible effect of VA on in-hospital outcome, and multivariate logistic regression models were used to adjust for age, gender, and comorbidities to see if the mortality effect of VA was confounded by these variables. Logistic regression models were also used to assess the effect of VA on other in-hospital adverse events such as recurrent ischemia, re-myocardial infarction, cardiogenic shock, congestive heart failure (CHF), major bleeding, and stroke. All analyses were performed using STATA version 9 (StataCorp LP, United States).

RESULTS

Of 5055 patients with ACS enrolled in the SPACE registry from December 2005 through December 2007, 168 (3.3%) developed VA during hospitalization of which 17 (1.2%) occurred at time of presentation to the hospital. The incidence of VA was significantly greater in patients with STEMI than in patients with NSTEMI/UA (6% vs 1.5%; *P*<.001). The mean age of all ACS subjects was 58 (12.9) years, and was similar in patients with and without VA (*P*=.72) (**Table 1**). A larger proportion of patients with VA were men compared with patients without VA (85.7% vs 77.2%; *P*=.004), and had a history of smoking (44.6% vs 32.0%; *P*<.001). Fewer patients with in-hospital VA had a history of hyperlipidemia (24.4% vs 42.0%; *P*<.001) and a history of coronary artery disease (33.9% vs 42.7%; *P*=.01). Other medical and personal history variables were similar between groups. On admission, patients with VA were significantly more likely than patients without VA to have Killip class >I (36.4% vs 20.1%; *P*<.001), systolic BP <90 mm Hg (15.5% vs 2.8%; *P*<.001), HR >100 bpm (22.1% vs 14.6%; *P*=.010), and left ventricular ejection fraction <35% (61.9% vs 33.6%; *P*<.001). A greater proportion of VA patients

Table 1. Baseline characteristics.

Characteristics	Total N (%)	Ventricular arrhythmia n (%)[a]	No ventricular arrhythmia n (%)	*P*
Total	5055	168 (3.3)	4887 (96.7)	
Mean age, years (SD)	58 (12.9)	57.7 (14.9)	58 (12.9)	.72
Men	3914 (77.4)	144 (85.7)	3770 (77.2)	.004
Diabetes mellitus	2935 (58.2)	93 (55.4)	2842 (58.3)	.25
Hypertension	2782 (55.0)	83 (49.4)	2699(55.2)	.18
Hyperlipidemia	2084 (41.4)	41 (24.4)	2043 (42.0)	<.001
Coronary artery disease	2145 (42.4)	57 (33.9)	2088 (42.7)	.014
Angina	1399 (40.2)	38 (31.7)	1361 (40.4)	.155
Myocardial infarction	915 (26.3)	21 (17.5)	894 (26.6)	.079
Cerebrovascular accident	309 (6.1)	14 (8.3)	295 (6.0)	.56
Percutaneous coronary intervention	698 (13.8)	17 (10.1)	681 (13.9)	.084
Coronary artery bypass graft	296 (5.9)	11 (6.5)	285 (5.8)	.87
Smoking	1637 (32.4)	75 (44.6)	1562 (32.0)	<.001
Clinical presentation				
Killip class >I	937 (20.6)	55 (36.4)	882 (20.0)	<.001
Heart rate >100	679 (14.9)	33 (22.1)	646 (14.6)	.010
Systolic blood pressure <90	148 (3.2)	23 (15.5)	125 (2.8)	<.001
Ejection fraction <35%	1149 (34.5)	70 (61.9)	1079 (33.6)	<.001
Diagnosis				
ST-segment elevation myocardial infarction	2096 (41.5)	125 (74.4)	1971 (40.3)	<.001
Non-ST-segment elevation myocardial infarction	1840 (36.4)	33 (19.6)	1807 (37.0)	<.001
Unstable angina pectoris	1119 (22.1)	10 (6.0)	1109 (22.7)	<.001
Median length of hospitalization, days	5	8	5	<.001

[a] Number and % of column total unless otherwise indicated.

compared with non-VA patients had STEMI (74.4% vs 40.3%), and a smaller proportion had NSTEMI (19.6% vs 37.0%) and UA (6.0% vs 22.7%; *P*<0.001 for all comparisons). Patients with VA were hospitalized for a median of 8 days, compared with 5 days for those without VA (*P*<.001).

Patients with VA were less likely than those without VA to receive the evidence-based therapies beta-blockers (62.3% vs 82.3%; *P*<.001), angiotensin-converting enzyme inhibitors (ACEI, 58.7% vs. 69.9%; *P*=.002), IV anticoagulant (77.4% vs 82.8%; *P*=.046), and statins (87.4% vs 93.5%; *P*=.003); while they were more likely to have elevated troponin (66.1% vs 62.4%; *P*<.001) (**Table 2**). No differences were observed in the rate of interventions between the two groups.

On multivariate regression analysis, male gender,

Table 2. In-hospital management.

Variables, n (%)	Total (N=5055)	Ventricular arrhythmia (n=168)	No ventricular arrhythmia (n=4887)	*P*
Treatment				
Aspirin	4929 (97.8)	160 (95.8)	4769 (97.8)	.08
Clopidogrel	4227 (83.9)	134 (80.2)	4093 (84.0)	.121
Beta-blocker	4115 (81.6)	104 (62.3)	4011 (82.3)	<.001
Angiotensin converting enzyme inhibitor	3504 (69.5)	98 (58.7)	3406(69.9)	.002
Angiotensin receptor blocker	297 (5.9)	6 (3.6)	291 (6.0)	.13
Statin	4705 (93.3)	146 (87.4)	4559 (93.5)	.003
Anticoagulant	4176(82.6)	130 (77.4)	4046 (82.8)	.046
IV insulin <24 h	479 (13.8)	27 (22.7)	452 (13.5)	.005
Troponin	3149 (62.5)	111 (66.1)	3038 (62.4)	<.001
Intervention				
Coronary angiogram	3397 (67.2)	100 (59.5)	3297 (67.5)	.05
Percutaneous coronary intervention	1776 (35.3)	62 (36.9)	1714 (35.2)	.49
Coronary artery bypass graft	425 (8.5)	17 (10.2)	408 (8.4)	.79

Values are number and percentage.

systolic blood pressure <90 mm Hg, Killip class, and positive cardiac markers were independently associated with an increased risk for AV, while therapy with a history of hyperlipidemia was associated with a decreased risk of VA (**Table 3**). In-hospital events and outcomes were more frequent in the presence of VA (**Table 4**). Mortality was significantly higher in VA patients (27.0%) compared with non-VA patients (2.2%; *P*=.001)(**Table 4**). The impact of VA on in-hospital mortality for the overall population and ACS subtype remained high; however, it was attenuated after adjusting for age, gender, and comorbidities (**Table 5**).

Table 3. Multivariate regression analysis of factors associated with in-hospital ventricular arrhythmia in acute coronary syndrome patients.

All ACS patients	Odds ratio	95% CI	P
Gender (male)	1.7	1.1-3.1	.040
Systolic blood pressure <90 mm Hg	6.3	3.4-11.5	<.001
Killip class >1	2.3	1.5-3.6	<.001
Positive cardiac markers	2.3	1.2-4.7	.018
Hyperlipidemia	0.49	0.3-0.7	<.001

DISCUSSION

The occurrence of VA in patients with ACS is of substantial importance in the clinical decision-making process. Large multinational studies have been conducted in recent years to determine the magnitude and prognosis associated with VA in patients hospitalized with ACS.[10] Our multicenter, prospective data expand this knowledge base to include the incidence, associated factors, and outcomes of patients with ACS complicated by the development of serious arrhythmias. In this study VA occurred in 6% of patients with STEMI and 1.5% in patients with NSTEMI/UA.

The incidence of VA during hospitalization for ACS in our study is similar to that reported in previous studies of patients with STEMI and NSTEMI enrolled in randomized clinical trials (RCT).[7] Additionally, RCT patients were more likely to be men[11-13] and have a history of coronary heart disease[14] and hyperlipidemia,[15]

Table 4. In-hospital outcomes in patients with acute coronary syndrome with and without ventricular arrhythmia (VA).

Hospital event	Total (N=5055)	VA (n=168)	No VA (n=4887)	P
Death	155 (3.1)	46 (27.0)	109 (2.2)	<.001
Recurrent ischemia	638 (12.6)	56 (33.3)	582 (11.9)	<.001
Re-myocardial infarction	77 (1.5)	10 (6.0)	67 (1.4)	<.001
Cardiogenic shock	222 (4.4)	65 (38.9)	157 (3.2)	<.001
Congestive heart failure	520 (10.3)	66 (39.3)	454 (9.3)	<.001
Major bleeding	68 (1.3)	10 (6.0)	58 (1.2)	<.001
Stroke	48 (1.0)	6 (3.6)	42 (0.9)	.004

Values are number and percentage.

Table 5. Impact of ventricular arrythmia on in-hospital death in acute coronary syndrome (ACS) patients.

	Odds ratio (95% CI)	P
All ACS	16.5 (11.2-24.9)	<.001
Age adjusted	18.6 (12.3-27.9)	<.001
Age and gender adjusted	20 (13.5-31.5)	<.001
Age, gender, and comorbidiesa adjusted	13.1 (7.2-24.1)	<.001
ST-segment elevation myocardial infarction	11.1 (6.9-17.7)	<.001
Age adjusted	13.1 (7.9-21.6)	<.001
Age and gender adjusted	13.7 (8.1-22.9)	<.001
Age, gender, and comorbidies[a] adjusted	11.1 (5.2-23.5)	<.001
Non-ST segment elevation myocardial infarction/Unstable angina pectoris	26.5 (12.9-53.9)	<.001
Age adjusted	22.5 (10.8-47.1)	<.001
Age and gender adjusted	26.3 (12.3-56.2)	<.001
Age, gender, and comorbidies[a] adjusted	14.1 (4.3-45.7)	<.001

[a] History of prior MI, PCI, angina, CABG, CVA, smoking, HTN, DM, and hyperlipidemia.

and have Killip class >I on admission. Our baseline findings revealed less coronary artery disease and hyperlipidemia compared with these published studies. Characteristics that were more frequent in our non-VA patients including a history of coronary disease (angina, MI), PCI, diabetes mellitus, and hypertension are similar to results from the GRACE Registry. Moreover, less frequent use of evidence-based therapies including ACEI, beta-blockers, statins, and IV anticoagulants in our patients with VA compared with those without VA is similar to results reported previously[8,16,17] The fact that more severely ill patients have increased complications, including VA, and may not tolerate medications such as ACEI and beta-blockers, may confound this finding.

Factors associated with an increased risk of developing VA during hospitalization for ACS were as follows: male gender, smoking, Killips class >I, higher HR, lower systolic blood pressure, and positive cardiac markers; while factors associated with a decreased risk were as follows: prior history of hyperlipidemia, MI, CAD, beta-blockers, ACEI, and statins. It is noteworthy that these associations varied among published studies, which may be attributed to differences in the population studied; for example, some share our observation of increased risk with Killip >I, positive cardiac marker, smoking, and high HR and decreased risk with prior MI.[8] Few studies, however, found prior PCI associated with decreased risk. Similarly, prior PCI in our study predicted a decreased risk for VA. In contrast, Mehta et al reported from the APEX AMI trial that VA is associated with a more than 3-fold greater risk of 90-day mortality in patients undergoing primary PCI.[18] The development of VA adversely influences the prognosis of patients with ACS. In our study, adverse events during hospitalization were more frequent in the VA group than in patients without VA. Interestingly, not only adverse events related to ischemia (recurrent ischemia and recurrent MI) and left ventricular dysfunction (CHF and cardiogenic shock) were significantly associated with the presence of VA, but other clinically relevant events (stroke and major bleeding) were also significantly increased in patients with VA. Therefore, patients with ACS who develop VA are at risk for cardiovascular and bleeding-related complications.[8]

In-hospital mortality rates were extremely high in patients with VA. Some of this association was related to older age, male gender, and a higher prevalence of comorbid conditions, as shown by attenuation of the risk after adjustment for these factors in multivariate regression. In examining the impact of VA in patients with STEMI, several investigators documented high mortality rates during hospitalization, which was our observation as well. Our results are similar to those of other studies, including descriptive studies, RCTs, and registry studies, which document a higher risk of death in patients who develop VA.[6,7,18] Therefore, timely identification of patients who are likely to develop a VA and proper management are crucial to improve prognosis for these patients.

A limitation of our study is that it was based on registry data which is a subject to missing data and selection biases inherent in the design of a registry. Moreover, the time of VA in relation to the revascularization and/or success of reperfusion therapy was not documented. This precludes ascertaining if patients with VA had not been reperfused or the VA developed before reperfusion therapy commenced. Therefore, our findings must be confirmed in future studies. Moreover, VA in our study included patients with VT and VF, which might have different prognostic implications in the setting of ACS; information with respect to the type of VA was not documented in our study. Finally, the pre-hospital VA and/or sudden death were not captured in this registry, which might underestimated the incidence of VA in our population.

In conclusion, information on the most powerful associated factors, such as an increased risk of VA occurring during hospitalization, is readily available in the patient's medical history, clinical presentation parameters, and laboratory findings at the time of hospital admission. This information can be used to identify patients at a greater risk for developing VA during hospitalization for ACS. As a complication of ACS, VA results in a poorer prognosis. Evaluating the simple risk factors identified in this study will aid in the decision-making process for daily clinical practice.

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The relationship between coronary artery calcification and myocardial perfusion in asymptomatic women

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BACKGROUND AND OBJECTIVES: No data are available in Saudi Arabia on the relationship between coronary artery calcification (CAC) and myocardial perfusion scintigraphy (MPS) in asymptomatic women, for determining subclinical coronary artery disease (CAD). The main objective of this study was to investigate the relationship between the presence of CAC and stress-induced myocardial ischemia by MPS in asymptomatic women.

DESIGN AND SETTING: Single-center retrospective study over a 2-year period.

METHODS: One hundred and one women (mean [SD] age, 56 [11] years) without known CAD underwent both MPS and CAC scanning within 3 months. The frequency of ischemia by MPS was compared with the presence or absence of CAC and the number of CAD risk factors.

RESULTS: The prevalence of ischemic MPS was 22% (22/101). Among the 22 patients with ischemic MPS, the CAC score was 0 in 5 patients of 22 (23%), 1 to 200 in 4 patients of 22 (18%), and more than 200 in 13 patients of 22 (59%) (*P*=.0001). In contrast, among the 79 patients with normal MPS, the CAC score was 0 in 44 of 79 (56%) patients, 1 to 200 in 25 of 79 (32%), and more than 200 in 10 of 79 (13%). The presence or absence of CAC was the single most important predictor of the MPS result (*P*=.0001).

CONCLUSIONS: Moderate to severe CAC is associated with ischemic MPS in more than 50% of asymptomatic women with 2 or more CAD risk factors. Abnormal MPS is rarely associated with a 0 CAC score. Normal MPS does not exclude subclinical CAD. Therefore, CAC screening is an appropriate initial screening test for CAD in asymptomatic women.

Currently available data continues to indicate an underrecognition and underdiagnosis of coronary artery disease (CAD) as a contributory factor in the high mortality rate in women.[1] The substantial under-representation of women in studies of noninvasive cardiac imaging further limits the evidence-based information that is used as a basis in clinical decision making.[2] Calcification of the coronary artery is virtually pathognomonic of atherosclerosis.[3-5] Clinical and histopathological studies have documented a close correlation between coronary artery calcification (CAC) detected by multi-detector computed tomography (MDCT) and atherosclerotic plaque burden.[6,7] In addition, a modest relationship between CAC and the severity of luminal stenosis has been revealed with the use of either conventional angiography[8,9] or intravascular ultrasound.[10,11] Some studies have suggested that the progression of CAD is more related to atherosclerotic plaque burden[12] rather than the extent of diseases detected by angiography.[13] CAC is an easily obtained surrogate for plaque burden, and it can detect coronary atherosclerosis in early stages based on the presences and severity of CAC.[14,15]

Stress myocardial perfusion single photon computed tomography (SPECT) is one of the most commonly performed noninvasive cardiac imaging tests in patients with known or suspected CAD. Gated myocardial perfusion scintigraphy (MPS) provides several parameters that are used to diagnose and risk stratify symptomatic and asymptomatic women. These parameters include stress-induced perfusion defects, global and regional left ventricular function, and left ventricular volumes.[16]

MPS using contemporary techniques has played an important role in the diagnosis and prognosis of CAD in women. In addition, myocardial perfusion imaging with exercise or pharmacologic stress has been shown to add incremental value to the use of clinical variables or exercise electrocardiogram stress testing alone in the risk stratification of women with an intermediate clinical pretest likelihood of CAD.[17] However, MPS imaging has been reported to have technical limitations in women, including false-positive results because of breast attenuation and small left ventricular function.[18] Furthermore, MPS is an expensive test and is not recommended for screening of asymptomatic women. Currently, little information is available as to whether CAC can identify asymptomatic women at high risk for myocardial ischemia. Accordingly, the purpose of this study was to determine the relationship between CAC score, number of cardiac risk factors, and the results of MPS in asymptomatic women.

METHODS

A retrospective study was performed on 101 women who underwent rest/stress MPS and CAC scanning within 3 months of each other between January 2009 and November 2010. Patients underwent MPS on a clinical basis for risk stratification, preoperative evaluation, or ongoing research project. CAC scanning was performed either on the basis of physician referral as a screening for subclinical CAD or an ongoing research project. Exclusion criteria included a history of myocardial infarction, prior coronary bypass surgery or percutaneous coronary intervention, prior cardiomyopathy, or known valvular heart disease. The study was approved by our hospital review board.

MPS acquisition and analysis

Patients underwent rest/stress myocardial perfusion studies with either a separate-day protocol or a same-day rest/stress sequence. The choice of tracer and same-day or separate-day protocol was based on logistical requirements. The rest dose in patients who underwent a separate-day rest/stress protocol was 10 to 370 megabecqurel (MBq) of technetium-99 (Tc-99m) sestamibi or tetrofosmin. The stress dose in patients who underwent the rest/stress same-day protocol was 1100 MBq of either (Tc-99m) sestamibi or tetrofosmin. Tc-99m sestamibi or Tc-99m tetrofosmin was injected either during peak treadmill exercise or during peak pharmacological vasodilatation with adenosine (140 μg/kg/min). SPECT imaging was started approximately 15 minutes following injection during exercise or at 30 minutes following pharmacological vasodilatation. Rest SPECT myocardial perfusion imaging was initiated at approximately 60 minutes following injection. SPECT imaging was performed with line source attenuation correction at 90° dual-detector gamma camera (Cardio MD, Philips Medical System, Milpitas, California) equipped with attenuation correction and truncation compensation. The acquisition parameters and post-processing were performed according to the most recent guidelines of the American Society of Nuclear Cardiology for nuclear cardiology procedures.[19]

All images were reoriented in short, vertical, and horizontal views utilizing AutoSPECT (Cedars-Sinai Medical Center, Los Angeles, California) for visual interpretation by an experienced nuclear medicine physician. The reader was not biased by clinical information and was unaware of the CAC score. Stress and rest perfusion images were scored using 17 tomographic segments, which included 6 segments each for the basal and midventricular slices, and 4 segments for the apical short-axis slices. The final segment was located on the most apical part of the left ventricle.[20] Finally, gated short-axis images were processed with the quantitative SPECT software to measure the ejection fraction. In the visual analysis, the 17 segments were scored for perfusion defects on a 4-point system (0=normal; 1=mild; 2=moderate; and 3=severe) for both the stress and rest images. From this analysis, ischemia was defined as a change in the segmental score between stress and rest. Segments with no change between stress and rest were classified as nonreversible. Summed stress and rest scores were calculated by summing the 17 segmental scores in each image set. Utilizing the summed difference score (SDS) in measuring defect reversibility was calculated from the difference between the summed stress and rest scores. An SDS lower than 2 was considered nonischemic, 2 to 7 was considered mild ischemia, and greater than 7 was considered moderate to severe ischemia. The reader made the final determination of an abnormal SPECT study by comparing both the perfusion and functional data.

Calcium scanning and interpretation

The imaging protocol involved acquiring a prospective electrographic-gated single scan on each patient consisting of approximately 30 to 40 slices of 2.5 mm each sufficient to cover the entire heart with triggering at 50% to 80% of the cardiac cycle. Breath-holding instructions were given to minimize misregistration. Scanning required a 3-mm CT slice thickness and a threshold for CAC of ≥130 Hounsfield units (HU) (CT density) involving ≥1 mm^2 area/lesion on the high

Table 1. Characteristics of the study population.

Parameter	Overall n= 101 women	Normal MPS n=79	Abnormal MPS n=22	*P*
Mean age (SD) (years)	56 (11)	56 (10)	56 (12)	.0021
Risk factors				
High Cholesterol[a]	24 (24)	19 (24)	5 (23)	.897
Diabetes[b]	45 (44.6)	33 (24)	12 (45)	.285
Hypertension[c]	52 (51.5)	36 (47)	16 (73)	.024
Smoking	23 (23)	19 (24)	4 (18)	.562
Positive family history	22 (22)	19 (24)	3 (14)	.295
CAC score				
0	49 (48.5)	44 (56)	5 (23)	<.0001
1-200	29 (32)	25 (32)	4 (18)	<.0001
More than 200	23 (23)	10 (13)	13 (59)	<.0001

Values are nymber and percent of column total except for age.
MPS=myocardial perfusion scintigraphy; CAC=coronary artery calcification.

[a] Defined as serum total cholesterol ≥230 mg/dL (6.2 mmol/L) or treatment with lipid lowering drugs.

[b] Defined as fasting blood sugar more than 126 dL (7 mmol/L) or treatment with insulin and or oral hypoglycemic drugs.

[c] Defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≤90 mm Hg and/or the use of antihypertensive medication.

definition 64-slice CT machine (GE Medical System, Waukesha, Wisconsin).

Foci of CAC were identified by an experienced radiographic technologist, confirmed by an experienced cardiovascular radiologist, and scored using semiautomatic commercial software on Advantage Workstation (GE Medical System). The software calculated lesion-specific scores as the product of the area of each calcified focus and peak CT number (scored as 1 if 131 to 199 HU; 2 if 200 to 299 HU; 3 if 300 to 399 HU; and 4 if 400 HU or greater) according to the Agatston method.[21] These were summed across all lesions identified within left main, left anterior descending, left circumflex, and right coronary arteries to provide arterial-specific calcium scores, and across arteries to provide the total CAC score.

Statistical analysis

Total calcium scores were classified into 3 categories: 0=calcium absent; 1 to 200=minimal to mild; and more than 200=moderate to severe; the prevalence of an ischemic MPS was compared across calcium score categories using the chi-square test for trend. A multiple logistic regression was performed to examine whether log (CAC +1) was independently associated with the likelihood of abnormal MPS result after adjustment for other CAD risk factors. All continuous variables are expressed as mean (SD). A value of $P<.05$ was considered to indicate a statistical significance.

RESULTS

The characteristics of the study population stratified by MPS are shown in **Table 1.** Of the 101 patients, 22 had abnormal MPS (22%) compared with normal MPS, and patients with abnormal MPS were significantly older and had significantly higher CAC. Interestingly, no significant correlation was observed between ischemic MPS and other traditional risk factors of CAD such as diabetes, hypertension, smoking, high cholesterol, or a positive family history for premature CAD. As shown in **Figure 1**, a very strong correlation was observed between the presence and the severity of CAC and MPS result. Only 5 patients (10%) out of 45 patients with zero CAC had abnormal MPS. However, patients with a CAC score of more than 200 had more than a 50% chance of having abnormal MPS ($P \leq .0001$).

A strong correlation was observed between the presence and the severity of CAC with age, diabetes, and hypertension, but no correlation was observed between CAC and high cholesterol, smoking, or family history. A total of 35 of 79 patients (45%) with normal MPS had CAC of more than zero. About 12.7% had severe CAC (CAC score more than 200) (**Figure 2**).

Diabetes was present in 45 patients of the total population study. A total of 17 of 45 patients (37.8%) had no detectable CAC, but 12 (26.7%) and 16 (35.6%) patients had a CAC score of 1 to 200 and more than 200, respectively, with statistically significant P value (.020). However, no correlation was observed between diabetes and abnormal MPS (P=.268). Multivariable logistic regression analysis showed that the log CAC score was the most and the only predictor for abnormal MPS, odds ratio 2, and P value of less than .001. Other traditional CAD risk factors, e.g., diabetes, hypertension. age, family history, and high cholesterol, were not predictors for abnormal MPS in a multivariate regression analysis.

DISCUSSION

The main finding of our study is a strong relationship between the CAC score obtained by MDCT and the presence of ischemia as measured by stress MPS. The CAC score can accurately classify patients into low-risk or high-risk groups in asymptomatic women. The absence of CAC or CAC score in less than 200 asymptomatic women is associated with a low probability of abnormal MPS; in contrast women with a CAC score of more than 200 and 2 or more CAD risk factors have more than a 50% chance of having an abnormal (e.g., ischemic) MPS. This result may be exploited to improve the selection and use of a more expensive test, such as MPS, for identifying asymptomatic women with high risk for cardiovascular events.

Predictors of Ischemic MPS

In our study, the best predictors of ischemic MPS were CAC score and age. For example, asymptomatic 58-year old or older females with a CAC score of more than 200 have a 50% or more chance of having abnormal MPS, but asymptomatic relatively younger females (e.g., 56-year old or younger) with a zero CAC score have less than a 10% chance of having an abnormal MPS. This result is consistent with previous studies that demonstrate that the angiographic extent and severity of CAD are closely related to the CAC score,[22,23] and the angiographic stenosis severity best predicts an abnormal MPS.[24] Overall, the data suggests that CAC is more sensitive than MPS in asymptomatic women in detecting subclinical atherosclerosis and subsequent risk factor modification.

The impact of CAD risk factors on CAC score

Using univariate analysis, our data suggests a clear association between CAC and age, diabetes, and hypertension; in contrast no relationship was observed between CAC and other CAD risk factors such as family history of premature CAD, smoking history, and high cholesterol. However, in a multivariate analysis the presence of CAC was the only predictor for abnormal MPS. It is well known that conventional risk factors do correlate with CAC[25] even though CAC is superior to conventional risk factors in predicting outcomes. Postmenopausal women present a striking example of the inability of conventional risk factor analysis to predict the presence or absence of subclinical atherosclerosis. A study by Hecht and Superko showed no difference in any lipid parameters or in the Framingham risk score between postmenopausal women with and without calcified plaques, rendering a therapeutic decision that is plaque-imaging based extremely problematic.[26]

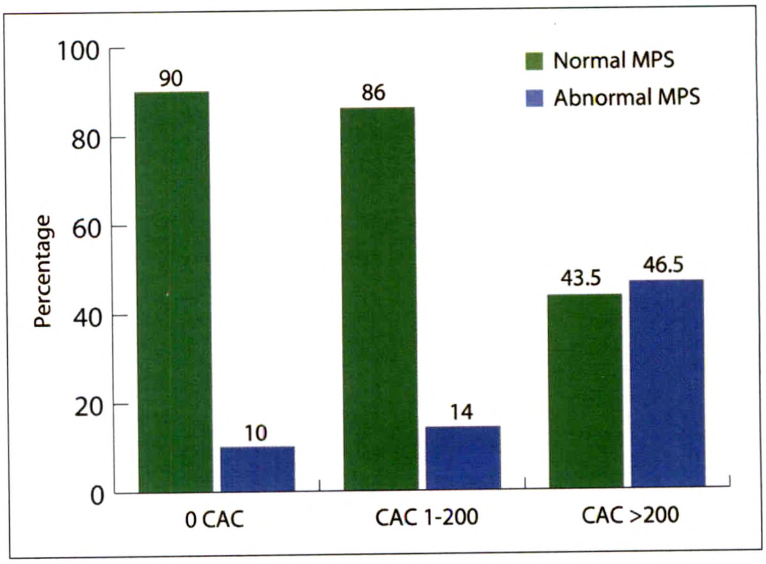

Figure 1. The frequency of abnormal (ischemic) stress single photon computed tomography (MPS) according to coronary artery calcification score (CAC).

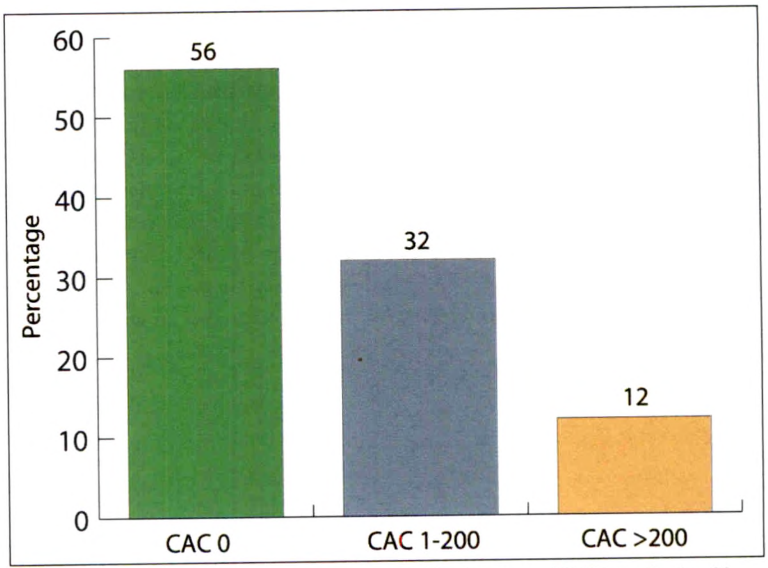

Figure 2. The distribution of coronary artery calcification score (CAC) in patients with normal stress single photon computed tomography (MPS) (*P*<.001 across all groups).

Normal MPS and presence of CAC

In our study approximately 45% of asymptomatic women with normal MPS have detectable CAC. In fact 13% have a CAC score of more than 200. This result indicates a limited role for all stress testing (e.g., stress MPS, stress echocardiography, or treadmill stress test) in asymptomatic women. Stress testing does not effectively screen for subclinical atherosclerosis. The presence of CAC implies atherosclerosis, but not necessarily the presence of coronary stenosis; in contrast MPS requires the presence of a hemodynamically significant lesion, either fixed or dynamic, before any abnormality becomes evident.[27]

Relationship between Diabetes, CAC, and MPS

Diabetic patients should be given special consideration because diabetes is considered a CAD risk equivalent. Our data showed a strong relationship between diabetes and CAC score ($P=.002$), but no statistical significance between diabetes and ischemic MPS was demonstrated. Diabetic patients with a zero CAC score have the same excellent prognosis as patients without diabetes, and it is reasonable to treat patients with a zero CAC scores less aggressively than would be dictated as a CAD risk equivalent. On comparison, diabetic patients with an elevated CAC score have a poor prognosis than patients without diabetes and a similar CAC score and subsequently should be treated more aggressively.[28]

Prior studies

This is the first study in Saudi Arabia to investigate the relationship between the CAC score and the MPS result. However, a few studies are available that investigate the interrelationship between CAC and MPS in the general population (men and women). He et al noted a threshold phenomenon with a very low abnormal MPS and a CAC score of less than 100 and 46% with abnormal MPS in patients with CAC score more than 400.[29] The observed difference in frequency of abnormal MPS (our patients with moderate to severe CAC have 56% abnormal MPS) in our study is due to many factors, such as gender and ethnic difference, and most importantly our patients have more risk factors for CAD, such as being older than 55 years, with a high prevalence of diabetes and other CAD risk factors. Another possible explanation for this difference is the criteria being utilized in the interpretation of MPS. Berman et al showed the same threshold phenomenon between CAC and MPS. He concluded that in most patients a low CAC score appeared to obviate noninvasive testing, but a normal MPS was frequently associated with coronary calcification that indicates subclinical atherosclerosis.[30] In our recently published data, a visual estimation of CAC on the CT component of positron emmission tomography (PET)-CT in cancer patients was highly consistent with the current study. We found that the presence of CAC by visual detection is associated with 53% abnormal MPS, but the absence of CAC was rarely associated with abnormal MPS.[31]

Study Limitations

The total study population was small (only 101 asymptomatic women) and patients with a CAC score of more than 200 was the smallest group (23 patients out of 101 of total study population). Another important issue was that our patients were asymptomatic and had multiple CAD risk factors, such as being older than 55 years and having diabetes. Further studies utilizing a larger patient population with fewer CAD risk factors are greatly needed.

In conclusion, CAC screening by MDCT in asymptomatic women with multiple risk factors predicts silent myocardial ischemia diagnosed by stress MPS. Therefore, CAC screening is recommended as an appropriate initial imaging test in this subset of patients for risk stratification. Further testing with more definitive testing, such as stress MPS, is recommended for patients with a CAC score of more than 200 with 2 or more CAD risk factors. Aggressive risk factor modification and therapy are highly recommended in low-risk patients with a CAC score of less than 200.

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original article

Relationship between obstructive sleep apnea severity index and left ventricular function and volume

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BACKGROUND AND OBJECTIVES: Obstructive sleep apnea (OSA) causes increased cardiovascular morbidity and mortality, including systemic arterial hypertension, coronary heart disease, heart rhythm and conduction disorders, heart failure and stroke. In our study, we aimed to assess left ventricular mass and myocardial performance index (MPI) in OSA patients.

DESIGN AND SETTING: A cross-sectional study conducted between May 2007 and August 2009 in a tertiary hospital in Istanbul, Turkey.

PATIENTS AND METHODS: Forty subjects without any cardiac or pulmonary disease referred for evaluation of OSA had overnight polysomnography and echocardiography. According to the apnea-hypopnea index (AHI), subjects were classified into three groups; mild OSA (AHI: 5-14/h; n=7), moderate OSA (AHI: 15-29/h; n=13), and severe OSA (AHI: ≥30/h; n=20). The thickness of the interventricular septum (IVS) and left ventricular posterior wall (LVPW) were measured by M-mode along with left ventricular mass (LVM) and LVM index (LVMI). The left ventricular MPI was calculated as (isovolumic contraction time + isovolumic relaxation time)/aortic ejection time by Doppler echocardiography.

RESULTS: No differences were observed in age or body mass index among the groups, but blood pressures were higher in severe OSA compared with moderate and mild OSA. In severe OSA, the thickness of the IVS (11.6 [1.7 mm]), LVPW (10.7 [1.7 mm]), LVM (260.9 [50.5 g]), and LVMI (121.9 [21.1g/m^2]) were higher than in moderate OSA (9.4 [1.3 mm]; 9.9 [1.6]; 196.4 [35.2]; 94.7 [13.2 g/m^2], respectively) and mild OSA (9.8 [2.4 mm], 8.9 [2.0 mm], 187.6 [66.2 g], 95.8 [28.6 g/m^2], respectively). In severe OSA, MPI (0.8 [0.2]) was significantly higher than in mild OSA (0.5 [*P*<.01]) but not significantly higher than moderate OSA (0.8 [0.1]).

CONCLUSIONS: OSA patients have demonstrable cardiac abnormalities that worsen with the severity of apnea. The MPI may have utility in subsequent OSA studies, possibly as a surrogate outcome measure.

Obstructive sleep apnea (OSA) is a serious, underdiagnosed disease[1,2] associated with increased cardiovascular morbidity and mortality, including systemic hypertension and pulmonary hypertension, coronary heart disease, heart rhythm and conduction disorders, and heart failure and stroke.[2-6] Given the strong link between OSA and hypertension, both left ventricular hypertrophy and left ventricular diastolic dysfunction (LVDD) are common echocardiographic abnormalities in OSA.[7]

Repeated episodes of hypoxemia, hypercapnia, and microarousal plus intrathoracic pressure fluctuations trigger mechanisms such as sympathetic hyperactivity,[8,9] oxidative stress,[10] systemic inflammation,[11] hypercoagulability,[12] and even endothelial dysfunction.[13] The prevailing hypothesis is that these abnormalities combine chronically to yield vascular lesions. The large arteries play a crucial role in cardiac structure, so increased arterial stiffness contributes independently to arterial pressure and to an increase in left ventricular afterload, thereby promoting left ventricular hypertrophy (LVH).[14]

Left ventricular diastolic dysfunction precedes left ventricular systolic impairment and accounts for 30% to 40% of overall patients with left ventricular failure.[15-17] Since systolic and diastolic dysfunctions frequently coexist, combined measures of left ventricular performance might be more reflective of overall cardiac dysfunction than systolic or diastolic measures alone. The Doppler-derived myocardial performance index (MPI also denoted the TEI-Doppler index), an index of combined systolic and diastolic functions, is defined as the sum of isovolumic contraction time and isovolumic relaxation time (IVRT) divided by the ejection time. Thus, MPI reflects global LV function as opposed to other measurements that reflect mainly either LV systolic or diastolic function.[18] The MPI is a sensitive index of symptomatic heart failure and predicts future development of heart failure independent of other echocardiographic measurements.[18] The MPI is a noninvasive, quick, and reproducible technique that can be used to evaluate left ventricular global function.[19]

Based on the above findings, we evaluated left ventricular mass (LVM) and left ventricular global function in OSA patients, including the relationship between apnea-hypopnea index (AHI) and MPI. This aim would allow us to test the hypothesis that OSA had important influences on cardiac functions as assessed by MPI. These data would allow us to explore the potential utility of the MPI in future OSA studies, eg, as a biomarker or to assess response to therapy or possibly as a robust marker of disease severity.

PATIENTS AND METHODS

Forty patients were referred to the sleep clinic between May 2007 and August 2009 with symptoms of nocturnal snoring and/or excessive daytime sleepiness. Patients who had known cardiac (including angina or arrhythmia) or lung disease, diabetes mellitus, angina pectoris, chronic renal and hepatic diseases, and serum electrolytes imbalances were excluded from the study. The Epworth sleepiness scale[20] was used to assess all participants; patients with a score above 10/24 (indicative of excessive daytime sleepiness) were recruited into the study. Blood pressure was measured according to European Society of Hypertension-European Society of Cardiology guidelines.[21] Hypertension was defined as a blood pressure >140/90 mm Hg. The heart rate (HR) per minute was measured in the sitting position and the body mass index (BMI) of the patients was calculated as weight divided by height squared (kg/m^2). A 12-lead surface electrocardiogram was taken from every subject to ensure normal sinus rhythm.

Overnight-attended polysomnography was performed in our sleep laboratory during which we obtained a 3-channel electroencephalogram (EEG), an electro-oculogram, and a submental electromyogram using surface electrodes. The airflow was measured by monitoring nasal pressure through nasal cannulae (Ultima Dual Pressure Sensor 0585. Braebon Medical Corporation. Carp. Ontario, Canada). The respiratory effort was measured by inductance plethysmography with transducers placed on the chest and abdomen (Respitrace, Ambulatory Monitoring, Ardsley, New York, USA). The arterial oxyhemoglobin saturation (SaO$_2$) was recorded with a pulse oximeter (Biox 3740, Ohmeda. Boulder, Colorado, United States). All variables were recorded continuously by a computerized data-acquisition system and stored electronically for later analysis (Sandman, Tyco Healthcare, Kanata, Ontario, Canada). All-night polysomnographic recordings were scored visually according to the Rechtschaffen and Kales (R and K) rules by experienced sleep scorers.[22] Briefly, sleep was scored as stage 1 to 4 non-rapid eye movement (NREM) or REM. Total sleep time (TST) was defined as the duration of sleep from "lights out" at the beginning of the study to "lights on" the following morning. Sleep latency was defined as the time from lights out to the first 30-second period of sleep. Sleep efficiency was defined as the TST expressed as a percent of the total study duration. Apnea was defined as the absence of airflow for ≥10 seconds associated with continued respiratory efforts (obstructive), absence of respiratory efforts (central), or features of central apnea followed by obstructive apnea (mixed). Hypopnea was defined as a 50% reduction in airflow for ≥10 seconds or a marked reduction in airflow associated with 4% oxygen desaturation and/or arousal from sleep. The number of apneas and hypopneas per hour of sleep were expressed as AHI. Arousal was defined as an abrupt shift of EEG frequency including alpha, theta, and/or frequencies greater than 16 Hz (but not spindles), lasting at least 3 seconds in duration and preceded by at least 10 seconds of stable sleep. Desaturations were accepted as a ≥4% decrease in oxygen saturation. Desaturation index (DI) was defined as the number of oxygen desaturation events per hour of sleep.[23]

All echocardiographic measurements were performed with the subjects in the lateral decubitus position using a 2.5 MHz probe. All echocardiographic examinations were performed by the same cardiologist who was blinded to the presence or absence of OSA. Ventricular diameters, volumes, and functions were measured according to the recommendations of the American Society of Echocardiography.[24] Basic measurements of left ventricular dimensions in diastole and systole, and thicknesses of interventricular septum (IVS), left ventricular posterior wall (LVPW), and LVM were measured by the M-mode technique; LVM was divided by body surface area to obtain LVM index (LVMI). The left ventricular ejection fraction (LVEF) was calculated by the Simpson method as (diastolic volume − systolic volume)/diastolic volume.

The early (E) and atrial (A) transmitral maximal flow velocities, the ratio (E/A), and the deceleration time of E-wave were registered. The IVRT was measured by the continuous wave Doppler technique. The velocity of mitral flow propagation was estimated using color Doppler M-mode. The left ventricular MPI was calculated as: (isovolumic contraction time + IVRT)/aortic ejection time. The global left ventricular dysfunction was defined as an MPI ≥0.50 [0.39 (0.05) normal level].[25]

Data were presented as mean (standard deviation), and the Kruskal-Wallis test was used for group comparisons. The Mann-Whitney U test was used when only two groups were compared. A *P* value <.05 was considered statistically significant.

Table 1. Basic characteristics of patients with obstructive sleep apnea (OSA) syndrome.

Patients with OSA	AHI 5-14/h	AHI 15-29/h	AHI ≥30/h	*P*
No. of subjects	7	13	20	
Mean age (years)	38.3 (6.1)	42.7 (9.1)	48.9 (7.4)	.01
Male, n (%)	4 (57.1)	10 (76.9)	17 (85.0)	NS
Female, n (%)	3 (42.9)	3 (23.1)	3 (15.0)	NS
Body mass index (kg/m²)	27.5 (5.1)	31.4 (4.6)	31.5 (4.9)	.275
Systolic blood pressure (mm Hg)	122.1 (12.7)	127.6 (17.6)	136.5 (18.2)	.005
Diastolic blood pressure (mm Hg)	75.3 (10.0)	78.5 (9.9)	81.4 (8.7)	.016
Heart rate (pulse/min)	92.9 (12.9)	86.4 (9.9)	87.7 (12.0)	.579
Hypertension, n (%)	1 (14.3)	4 (30.8)	10 (50.0)	.005
Apnea-hypopnea index (AHI) (per hour)	8.5 (2.2)	21.5 (3.8)	50.5 (15.3)	.001
Desaturation index (per hour)	9.8 (8.4)	22.0 (6.0)	39.7 (18.4)	.001
Minimum saturation of nocturnal arterial oxygen (SaO_2) (%)	87.3 (8.9)	85.3 (4.2)	75.7 (8.3)	.001
Average SaO_2 (%)	96.1 (1.8)	94.2 (1.9)	91.6 (4.2)	.001
Sleep duration (%) [a]	8.6 (11.9)	2.5 (5.0)	18.5 (22.7)	.002

Data are presented as n, n (%), or mean SD.

[a] At SaO_2 <90%

RESULTS

A total of 31 males (77.5%) and 9 females (22.5%) were included in the study. Patients were classified into three subtypes according to their AHI scores; mild (AHI 5-14 events/h), moderate (AHI 15-29 events/h), and severe (AHI ≥30 events/h). Twelve percent of patients were using alcohol and 42% of patients were cigarette smokers. Basic characteristics of the patients with OSA are shown in **Table 1**. No significant differences were observed in their sex, BMI, and HR among the OSA patients (*P*>.05). However, mean of age, systolic blood pressure , and diastolic blood pressure were higher in severe OSA patients than in moderate and mild OSA patients. Of the 40 OSA patients, 15 were hypertensive and the majority (50%) were in the severe group. As expected, AHI and DI were highest in patients with severe OSA (*P*<.0001), and these patients had both the lowest average and nadir oxygen saturation (SaO_2) (*P*<.0001). The percentage of sleep duration at <90% SaO_2 was significantly higher in the severe OSA group, while it was the lowest in the mild OSA group.

Basic echocardiographic measurements of the left ventricle in patients with OSA are shown in **Table 2**. The left atrial diameter and left ventricular end-diastolic and end-systolic diameters were not statistically different among groups of OSA patients in severe OSA patients. The thickness of IVS, LVPW, LVM, and LVMI were higher than both the moderate and mild OSA patients. Basic measurements in the different OSA groups are shown in **Table 3**.

The left ventricular systolic and diastolic functions in patients with OSA are shown in **Table 4**. The left ventricular systolic function was not significantly different in the three groups of OSA patients and was within normal limits. While mild OSA patients had normal left ventricular diastolic function, moderate and severe OSA patients had LVDD. The left ventricular MPI was significantly higher in severe OSA patients than in mild OSA patients (*P*=.01), but it was not statistically different between mild and moderate OSA patients (*P*>.05).

A positive correlation was shown between left ventricular MPI and AHI reflecting the severity of OSA (*P*=.001, r = 0.33). The correlation between MPI and AHI in OSA patients is shown in **Figure 1**.

DISCUSSION

OSA has important influences on cardiac functions such as left/right ventricular dysfunction, cardiac arrhythmia, and pulmonary hypertension.[26] Since these dysfunctions are closely related with cardiac and systemic complications, we need a reproducible, widely applicable, and a simple noninvasive method for the estimation of left ventricular global function in patients with OSA. For this purpose, we investigated LVM and left ventricular global function in OSA patients by MPI including the relationship between AHI and MPI. These data would allow us to explore the potential utility of the MPI in future OSA studies.

Although the mechanism of impairment in myocardial contraction and relaxation seen in patients with OSA is poorly understood, OSA may increase cardiac risk due to an imbalance of myocardial oxygen demand and supply as a result of hypoxemia, hypercapnia, and increased sympathetic activation occurring during apnea.[27] Diseases, such as hypertension, obesity, and diabetes mellitus, which often accompany OSA, also contribute to the development of LVH. In our study, diabetes mellitus and coronary artery disease were excluded and no significant differences were observed in BMI between the patient groups. However, in our study, 15 of 40 OSA patients were hypertensive, and the majority (50%) were in the severe OSA group. Because of the compelling evidence of a causal link between OSA and hypertension, we believe that it would be inappropriate to exclude hypertensive patients from these analyses since the causal pathway underlying LVDD from OSA may well involve hypertension. In a study by Lavie et al[28] in 2677 people attending a sleep clinic, the relationship between the severity of OSA significantly contributed to hypertension independent of all known confounding variables. Each apneic event per hour of sleep added about 1% to the risk of having hypertension. Apnea and hypopnea cause temporary elevations in blood pressure in association with blood oxygen desaturation, arousal, and sympathetic activation and may cause elevated blood pressure during the daytime and ultimately sustained hypertension.[29] In our patients, the percentage of sleep duration <90% SaO_2 was the highest in the severe OSA group, while it was the lowest in the mild OSA group. The severe OSA patients had more hypoxic duration in their sleep compared with the moderate and mild OSA groups. Because OSA may cause hypertension that may then lead to LVH, we do not view the imbalance of blood pressure between groups as a confounder, but rather an important factor on the causal pathway of interest.

In this study, IVS and LVPW diameters and LVM and LVMI were slightly higher in severe OSA patients, whereas they were within normal limits in mild and moderate OSA patients. Moreover, severe OSA patients had slight LVH. Our study did not define the mechanism underlying LVH; however, LVH could be caused by hypertension, intermittent blood pressure surges, and/or nocturnal hypoxemia. Noda et al[30] re-

Table 2. Echocardiographic measurements of the left ventricle in patients with obstructive sleep apnea (OSA) syndrome.

Patients with OSA	AHI 5-14/h	AHI 15-29/h	AHI ≥30/h	*P*
No. of subjects	7	13	20	
Thickness and diameters				
Left atrium (19-40 mm)[a]	37.0 (5.1)	36.2 (3.4)	37.5 (4.1)	.619
Interventricular septum thickness in diastole (6-11 mm)[a]	9.8 (2.4)	9.4 (1.3)	11.6 (1.7)	.004
Posterior left ventricular wall thickness in diastole (37-56 mm)[a]	8.9 (2.0)	9.9 (1.6)	10.7 (1.7)	.033
Left ventricular end-diastolic diameter (37-56 mm)[a]	46.2 (4.7)	46.7 (6.3)	49.5 (4.2)	.278
Left ventricular end-systolic diameter (19-40 mm)[a]	28.7 (4.4)	29.5(4.4)	31.2 (3.4)	.383
Left ventricular mass				
Left ventricular mass[b]	187.6 (66.2)	196.4 (35.2)	260.9 (50.5)	.001
Left ventricular mass index[b]	95.8 (28.6)	94.6 (13.2)	121.9 (21.1)	.020

Data are presented as mean (SD) or n. AHI: Apnea-hypopnea index
[a]Normal values; <198 g in females, <294 g in males; [b]<110 g/m^2 in females, <134 g/m^2 in males.

Table 3. Statistical comparison of the basic measurements in the different obstructive sleep apnea syndrome groups.

	Group 1 vs 2[a]	Group 2 vs 3[a]	Group 1 vs 3[a]
Systolic blood pressure	.145	.017	.006
Diastolic blood pressure	.281	.042	.011
Interventricular septum thickness in diastole	.498	.001	.090
Posterior left ventricular wall thickness in diastole	.150	.111	.019
Left ventricular mass	.452	.001	.017
Left ventricular mass index	.937	.001	.043
Myocardial performance index	.001	.495	.001

Data are presented as *P* values obtained using the Mann-Whitney U test.
[a]Group 1: apnea-hypopnea index (AHI)=5-14, Group 2: AHI=15-29, Group 3: AHI=≥30.

Table 4. Left ventricular functions by echocardiography in patients with obstructive sleep apnea syndrome.

	AHI 5-14/h	AHI 15-29/h	AHI ≥30/h	*P*
N	7	13	20	
Left ventricular ejection fraction in two dimensions by Simpson's method 55-75%[a]	67.4 (7.9)	67.6 (4.9)	66.1 (5.6)	.514
Early mitral flow velocity (m/sec)	0.8 (0.1)	0.7 (0.2)	0.7 (0.2)	.601
Atrial mitral flow velocity (m/sec)	0.7 (0.2)	0.6 (0.2)	0.7 (0.2)	.481
Ratio of early and atrial mitral flow velocity >1[a]	1.2 (0.3)	1.2 (0.4)	1.0 (0.3)	.369
Mitral deceleration time, <220[#] (m/sec)[a]	220.6 (46.5)	224.3 (54.5)	225.8 (64.0)	.965
Isovolumic relaxation time, <100[#] (m/sec)[a]	75.1 (10.2)	100.4 (19.7)	105.0 (19.3)	.002
Myocardial performance index, 0.39 (0.05)[a]	0.5 (0.1)	0.8 (0.2)	0.8 (0.2)	.001

Data presented as mean (SD).
AHI: Apnea-hypopnea index
[a]Normal values.

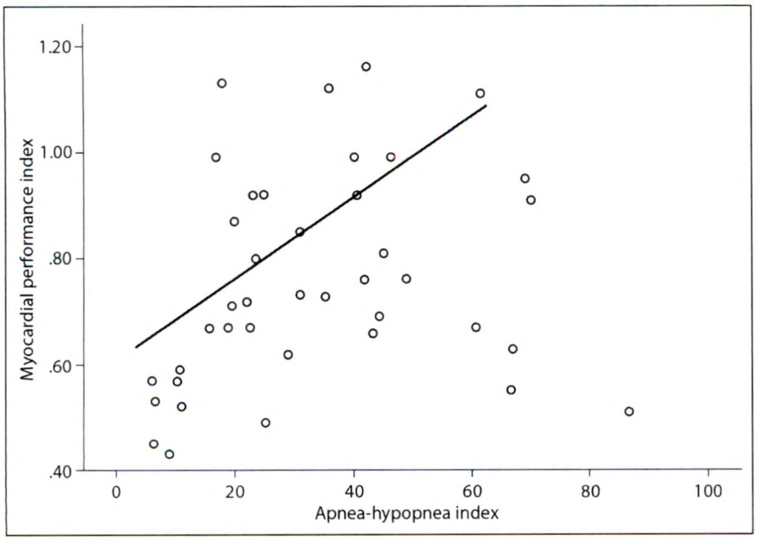

Figure 1. Correlation between myocardial performance index (MPI) and apnea-hypopnea index (AHI) in obstructive sleep apnea syndrome patients (r=0.33; *P*<.05).

ported echocardiographic evidence of LVH in 50% of patients with an AHI >20 per hour compared with 21.4% in those with an AHI <20 per hour.

In our study, we found that moderate and severe OSA patients had LVDD and also had global dysfunction diagnosed with increased MPI, although they had normal LVEF. In contrast, Laaban et al[31] suggested that OSA may be a direct cause of daytime LV systolic dysfunction. However, several cross-sectional studies[32,33] concordant with our results have demonstrated that the daytime LVEF was normal in patients with OSA and did not significantly differ between patients with OSA and control subjects. In theory, the discordance between our study and Laaban's study may be because of our relatively small sample size or perhaps because of a high risk of technical failure of echocardiography in patients with severe obesity. We would advocate for future studies using radionuclide angiography or cardiac magnetic resonance in a large group of OSA patients.

The mechanisms underlying diastolic dysfunction in OSA patients are not clear; however, elevations in nocturnal blood pressure and sympathetic nervous system activity[34] in OSA subjects create ventricular pressure overload.[35] It could be speculated that as it occurs in other processes, such as chronic hypertension and aortic stenosis, increased pressure overload at the cellular level would mainly result in decreased levels of sarcoplasmic reticulum calcium adenosine triphosphotase pump, and increased phospholamban.[36] This process could slow the removal of calcium from the cytosol, which leads to impaired ventricular relaxation. However, the pressure overload causes activation of multiple cellular signals that create myocardial tissue hypertrophy and interstitial fibrosis, increasing passive stiffness.[37] Indeed an impaired coronary flow reserve would cause silent ischemia, worsening ventricular active relaxation when left ventricular diastolic pressure begins to rise.

Another plausible mechanism to explain the presence of diastolic dysfunction is related to futile inspiratory efforts.[38] These efforts result in exaggerated negative intrathoracic pressure, which leads to an increase in left ventricular transmural pressure and hence afterload without increasing blood pressure. Another consequence of the increased negative intrathoracic pressure is the leftward shift of the IVS related to enhanced venous return and right ventricle dilatation. All of the aforementioned effects of the enhanced negative intrathoracic pressure have been demonstrated to affect left ventricular filling.[35] It is difficult to define how each of those mechanisms affects diastolic function in a single OSA patient because of their complex interactions. However, in the initial stages of the disease, we hypothesize that mechanical effects of obstructive events mainly create ventricular pressure overload that by itself might lead to slowed ventricular relaxation.

Our study has strengths, including its novelty, but we acknowledge a number of limitations. We had a relatively small sample size and thus we were likely underpowered for some of our assesements particularly in subgroup analyses. We also realize that a number of covariates are present such that we are unable to distinguish the effects of severe OSA from those of hypoxemia. Although hypertension is quite prevalent among those with severe OSA, we would argue that hypertension may be on the causal pathway from OSA to LVH, such that it may be inappropriate to control for hypertension or to exclude it. That is, if we were to select severe OSA patients without hypertension, we may be choosing those patients who are somewhat resistant to OSA consequences. Ultimately, we acknowledge that control of BMI and hypertension in future studies as well as controlled interventional studies will be required to show the isolated effect of AHI on the measured parameters and to draw rigorous conclusions. However, we believe that our data represent an important addition to the published studies based on their novelty and the hypotheses that we have generated for subsequent research. We believe the MPI may have utility in subsequent OSA research, potentially as a surrogate outcome measure.

In conclusion, we found that the OSA may result in left ventricular dysfunction. A strong positive correlation was observed between MPI and severity of OSA. The MPI is a reproducible, widely applicable, and a simple noninvasive method for the estimation of left ventricular global function in patients with OSA. Since the ventricular function provides prognostic information in patients, the results from this study should be further confirmed with several longitudinal studies.

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The relationship between markedly elevated glucose challenge test results and the rate of gestational diabetes mellitus and gestational impaired glucose tolerance

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BACKGROUND AND OBJECTIVES: Even though the 50 g oral glucose challenge test (GCT) is the most commonly used screening modality for gestational diabetes mellitus (GDM), no consensus for the diagnostic approach is available to patients with a markedly elevated GCT result. We aimed to evaluate the diagnostic utility of markedly elevated GCT results and the impact of age using the oral glucose tolerance test (OGTT) as gold standard.

DESIGN AND SETTING: Retrospective study conducted in a women's hospital in Ankara, among patients who underwent GCT from January 2005 to December 2008.

PATIENTS AND METHODS: In this retrospective study, we included 626 pregnant women who underwent a 3-hour 100 g OGTT after a GCT result ≥180 mg/dL among 29 842 women. We calculated positive predictive values (PPV) of each GCT category to diagnose GDM and both GDM and gestational impaired glucose tolerance (GIGT).

RESULTS: A GCT result of ≥240 mg/dL provided 100% PPV for the diagnosis of GDM and a result of >230 mg/dL provided 100% PPV for the diagnosis of GDM + gestational impaired glucose tolerance (GIGT), according to both, National Diabetes Data Group (NDDG) and Carpenter and Coustan (CC) criteria. A result of ≥200 mg/dL provided 100% PPV for diagnosing GDM+GIGT in patients older than 35 years, according to the CC criteria.

CONCLUSIONS: The GCT result of 200 mg/dL is an ideal cutoff value for the diagnosis of GDM + GIGT in patients ≥35years, and OGTT can be omitted in these patients. In younger patients, the cutoff value should be chosen as 230 mg/dL.

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of varying degrees of severity with onset or first recognition during pregnancy.[1] Approximately, 7% of all pregnancies (the prevalence ranges 1% to 14% depending on ethnicity) are complicated with GDM.[2] GDM is associated with increased fetal and maternal morbidity; therefore, a correct diagnosis is important,[3] but overdiagnosis increases medical costs and maternal anxiety.[4] There are controversies about diagnostic tests and criteria for GDM.[5,6] Since the oral glucose tolerance test (OGTT) is time consuming, expensive, and inconvenient, easier tests with the same diagnostic value have been studied.[7-11]

The 50 g oral glucose challenge test (GCT) is the most commonly used laboratory screening modality for GDM in many parts of the world.[5] It is easily tolerated among the majority of the pregnant women and can be performed at any time during the day because fasting is not required. Different screening thresholds have been utilized with varying sensitivities,[2] but there is no consensus on a diagnostic approach to patients with a markedly elevated GCT result.

In 1982, Carpenter and Coustan (CC) reported that patients with a GCT result of more than 182 mg/dL had a 95% chance of having GDM.[7] The 2003 Canadian Diabetes Association guidelines recommended diagnosing GDM if the glucose level 1 hour after the GCT is 190 mg/dL.[12] However, the American Congress of Obstetricians and Gynecologists (ACOG) guidelines for GDM advised GCT only for screening purposes and did not define any threshold.[3] Even though there is a lack of consensus in patients with markedly elevated screening results, there is a tendency to diagnose GDM, especially, with GCT results ≥200 mg/dL.[13] Our aim in this study was to evaluate the association between markedly elevated (≥180 mg/dL) GCT results and OGTT for the diagnosis of GDM and gestational impaired glucose tolerance (GIGT) according to both National Diabetes Data Group (NDDG) and CC criteria and whether this association differs in different age groups.

PATIENTS AND METHODS

This retrospective study was approved by the ethics committee of our hospital. We retrieved the records of patients who underwent a GCT between the years 2005 and 2008 from the hospital information system. We found 29 842 women who fulfilled the criteria. Among these women, 626 women with a GCT result ≥180 mg/dL underwent OGTT. These patients comprised the study group. We screened for GDM in all nondiabetic pregnancies using a 2-step standard protocol. At 24 to 28 weeks, all pregnant women without previously diagnosed diabetes were offered screening for GDM with a 1-h 50 g GCT during a routine prenatal visit, regardless of the time or the fasting. In this study, all the patients underwent both GCT and OGGT. The results of GCT and OGTT were not influenced by each other.

We reviewed the results according to both NDDG (8 patients) (plasma glucose thresholds: fasting 105 mg/dL, 1-h 190 mg/dL, 2-h 165 mg/dL, 3-h 145 mg/dL) and CC criteria (8 patients) (plasma glucose thresholds: fasting 95 mg/dL, 1-h 180 mg/dL, 2-h 155 mg/dL, 3-h 140 mg/dL). By both criteria, GDM is defined as at least two plasma glucose measurements at or higher than the reported cutoff values. GIGT is defined as a 1 plasma glucose measurement at or higher than the reported cutoff values during the diagnostic test.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) (SPSS Inc, Chicago, IL, USA) version 10. Receiver-operator characteristic (ROC) curves were generated and areas under the curve (AUC) were calculated for each data set of GDM, and both GDM and GIGT were diagnosed by NDDG and CC criteria. The significance of AUCs were controlled with Bonferroni Corrections (type I error rate=0.05/4=0.0125). For the purpose of analysis, screening test results were categorized by 10 mg/dL increments. We investigated positive predictive values (PPV) of each GCT category to diagnose GDM and GDM + GIGT, according to the NDDG and CC criteria. The cutoff points were computed if all the patients were diagnosed as GDM and GDM + GIGT (100% PPV) in a given 50 g GCT results. We further investigated cutoff points of GCT results in patients ≥35 years of age.

RESULTS

The mean (standard deviation) age of subjects were 31.4 (5.9); 11% (n=69) were less than 25 years old, 59.6% (n=373) were 25 to 34 years, and 29.4% (n=184) were equal to or more than 35 years old. Thirty-four percent subjects (n=213) had GDM, 53% (n=332) had GDM + GIGT by NDDG criteria, and 48.1% (n=301) had GDM, and 73.3% (n=396) had GDM + GIGT by CC criteria. The diagnosis of GDM was confirmed in only 25.4% of patients according to the NDDG criteria and 37.7% according to the CC criteria with GCT results between 180 and 189 mg/dL, and 39.5% of patients according to the NDDG criteria and 60.5% according to the CC criteria with GCT results between 200 and 209 mg/dL. A GCT result of ≥240 mg/dL provided 100% PPV for the diagnosis of GDM according to both criteria and was chosen as cutoff points (**Table 1**). For GDM and GIGT together, the diagnosis was confirmed in 40.7% of the patients according to the NDDG criteria, 50.8% according to the CC criteria with GCT results between 180 and 189 mg/dL, 65.4% according to the NDDG criteria, and 74.1% according to the CC criteria with GCT results between 200 and 209 mg/dL. A GCT result of ≥230 mg/dL provided 100% PPV for the diagnosis of GDM + GIGT according to both criteria (**Table 1**).

The AUC calculated by the ROC curve analysis of GCT results ≥180 mg/dL for diagnosing GDM and GDM + GIGT using NDDG and CC criteria are given in **Table 2**. The AUC for GDM using the NDDG and CC data were 0.653 and 0.658, which are statistically significant ($P<.0001$ and $P<.0001$, respectively). The AUC for GDM + GIGT using NDDG and CC criteria were 0.674 and 0.680, which are statistically significant ($P<.0001$ and $P<.0001$, respectively). ROC curves of each analysis are given in **Figure 1**.

In patients ≥35 years, a GCT result of ≥220 mg/dL provided 100% PPV for the diagnosis of GDM according to both criteria, and for the diagnosis of GDM + GIGT according to the NDDG criteria. A result of ≥200 mg/dL provided 100% PPV for diagnosing GDM + GIGT in patients older than 35 years according to the CC criteria and was chosen as the cutoff point (**Table 3**). The AUC calculated by the ROC

Table 1. Rate of GDM and GDM + GIGT diagnosed according to GCT results using NDDG criteria and Carpenter and Couston criteria in all ages.

National Diabetes Data Group									
	GDM				GDM + GIGT				
		+	-	Total			+	-	Total
GCT	≥240	6 (100%)	0	6	GCT	≥230	10 (100%)	0	10
	<240	207 (33.4%)	413 (66.6%)	620		<230	322 (52.4%)	294 (47.6%)	616
	Total	**213 (34%)**	**413 (66%)**	**626**		**Total**	**332 (53%)**	**294 (47%)**	**626**
Carpenter and Coustan criteria									
	GDM				GDM + GIGT				
		+	-	Total			+	-	Total
GCT	≥240	6 (100%)	0	6	GCT	≥230	10 (100%)	0	10
	<240	207 (33.4%)	413 (66.6%)	620		<230	322 (52.4%)	294 (47.6%)	616
	Total	**213 (34%)**	**413 (66%)**	**626**		**Total**	**332 (53%)**	**294 (47%)**	**626**

GDM: Gestational diabetes mellitus; GIGT: gestational impaired glucose intolerance; GCT: glucose challenge test.

curve analysis of GCT results ≥180 mg/dL for patients older than 35 years for diagnosing GDM and GDM + GIGT using NDDG and CC criteria are given in **Table 4**. The AUC for GDM using the NDDG and CC data were 0.599 and 0.597, which are statistically not significant because of Bonferroni corrections (P=.0293 and P=.0331, respectively). The AUC for GDM + GIGT using NDDG criteria was 0.629, which is statistically significant (P=.0070), and the AUC for GDM + GIGT using CC criteria was 0.630 (P=.0127), which is has borderline statistical significance after Bonferroni correction. ROC curves of each analysis are provided in **Figure 2**.

Table 2. Receiver-operator characteristic curve analysis of GCT results ≥180 mg/dL for diagnosing GDM and GDM + GIGT using NDDG and CC criteria in all patients.

Criteria	Diagnosis	AUC	95% CI	*P*
NDDG	GDM	0.653	0.604-0.703	<.0001
	GDM + GIGT	0.674	0.627-0.716	<.0001
CC	GDM	0.658	0.613-0.703	<.0001
	GDM + GIGT	0.680	0.635-0.725	<.0001

GCT: Glucose challange test; GDM: gestational diabetes mellitus; GIGT: gestational impaired glucose intolerance; NDDG: National Diabetes Data Group; CC: Carpenter and Coustan; AUC: area under curve; CI: confidence interval.

DISCUSSION

OGTT is designed on the basis that the diabetogenic stress of pregnancy is best recognized in the fed state. OGGT has become established as the gold standard diagnostic test for gestational diabetes. However, it is time consuming, expensive, and unpleasant; therefore, new and easy diagnostic tests need to be validated against OGTT.[5]

Two main criteria, NDDG and CC, are commonly used to examine 3-h OGTT. In 1964, O'Sullivan and Mahan[14] for the first time suggested that pregnancy glucose values obtained during a 100 g 3-h OGTT should be used to diagnose GDM. In 1979, the NDDG recommended new diagnostic thresholds, and most laboratories changed from using venous whole blood samples to using plasma or serum samples.[1] In 2000, the American Diabetes Association (ADA) revised the recommendation for the GDM diagnostic criteria and proposed adoption of CC thresholds, which represented the most accurate conversion of the O'Sullivan and Mahan criteria, rather than the NDDG thresholds, to reduce the risks of adverse perinatal outcomes attributable to GDM.[15] The prevalance rates of GDM have been increased by using CC criteria.[16,17] ACOG and ADA currently recommend the use of CC criteria.[2,3]

In this study, we investigated the PPV of GCT resuts ≥180 mg/dL for diagnosing GDM and both GDM and GIGT according to the NDDG and CC criteria in Turkish pregnant women. The PPV of GCT result between 180 to 189 mg/dL was only 25.4% according to the NDDG diagnostic criteria, and 37.7% according to the CC diagnostic criteria. We reached 100% PPV at the GCT level of 240 mg/dL and greater according to both criteria. When we considered the predictive value of GCT for diagnosing both GDM and GIGT, we reached 100% PPV at the GCT level of 230 mg/dL and greater according to both criteria.

Several studies have been performed in establishing

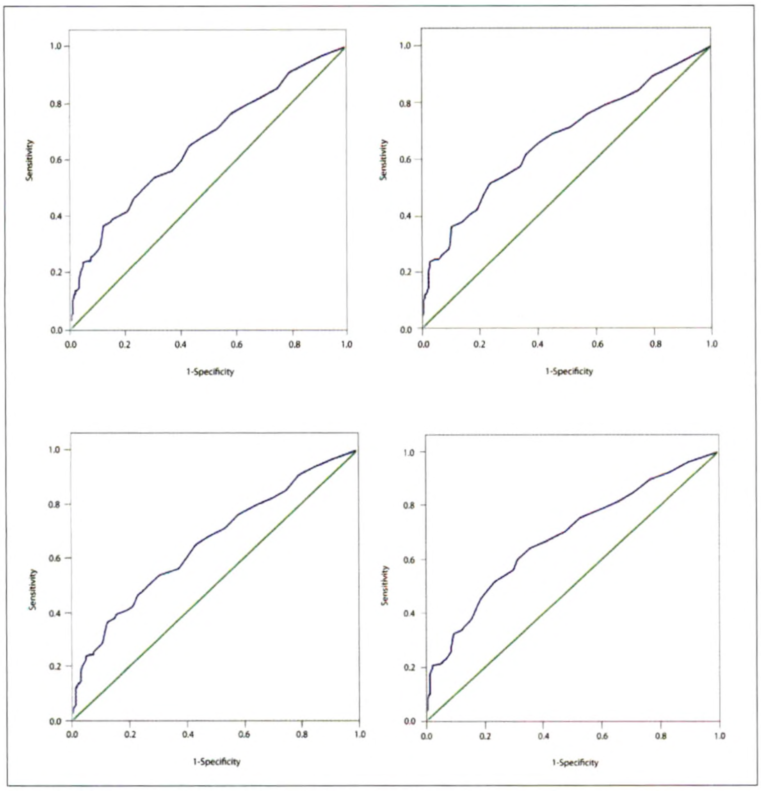

Figure 1. ROC curves for diagnosing GDM and GDM+GIGT using NDDG and CC criteria in all ages.

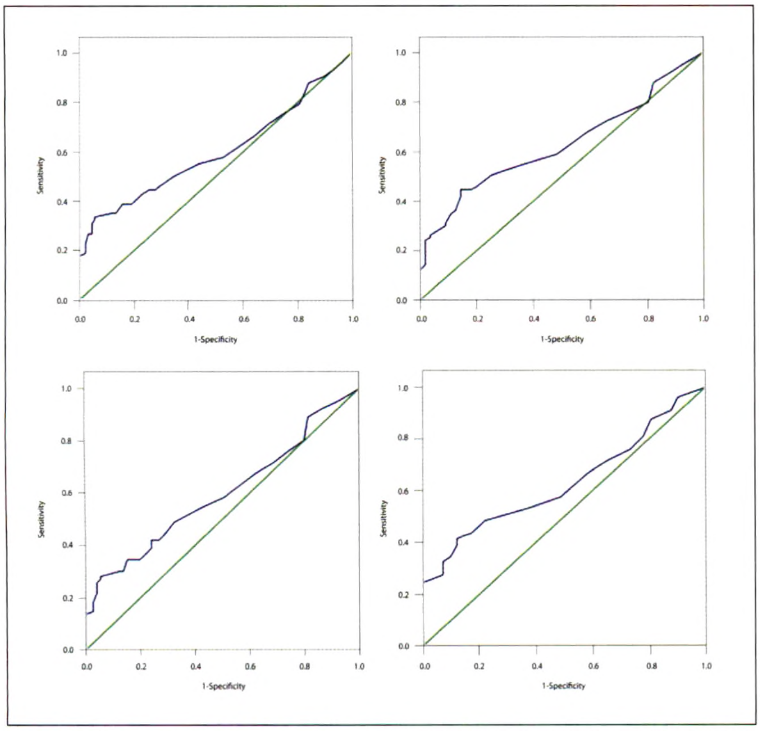

Figure 2. ROC curves for diagnosing GDM and GDM+GIGT using NDDG and CC criteria in patients ≥35 years.

the diagnostic value of markedly elevated GCT levels for gestational diabetes.[7-11] Lanni and Barrett reported that a cutoff value 200 mg/dL predicted only 47% to 54% of GDM cases, so it was inappropriate for GDM to be diagnosed based on the GCT, and this might lead to overdiagnosis.[10] Cheng et al reported 100% PPV for GCT results ≥230 mg/dL for diagnosing GDM according to the CC criteria, which was similar to our findings.[11]

The prevalence of GDM differs depending on the population being screened. In studies conducted in North America, the prevalence was higher in Asian, African American, Native American, and Hispanic compared to non-Hispanic white patients.[16] Because of variations in the prevalence based on ethnicity, it has been suggested that race-specific glucose screening test thresholds should be used.[18] Esakoff et al reported different sensitivity and specificity results for GCT in different ethnic groups.[19] Dooley et al defined a 90% risk of GDM with GCT result ≥200 mg/dL in nonwhite women, but the risk in white women was 66%.[9] Based on these findings, it is logical that different cutoff levels may be accepted in different ethnic groups for diagnosing GDM without performing further OGGT. One of the studies conducted in Turkey reached 100% specificity after a cutoff value of 221 mg/dL, which was lower compared to our findings.[20] Besides ethnicity, one of the major risk factors for GDM is increased maternal age.[16,17] Therefore, we investigated whether the PPV of GCT levels for GDM diagnosis differ in different age groups and we further analyzed our results according to age. After analyzing patients older than 35 years, we reached 100% PPV at the GCT level of 200 mg/dL or greater for diagnosing both GDM and GIGT according to the CC criteria. Our results showed that 100% PPV can be reached with lower GCT results in patients older than 35 years.

An important limitation regarding GCT results is low reproducibility. Only 83% of abnormal results were reproducible the next day in a study by Espinosa de los Monteros et al.[21] This was attributed to the fact that the reproducibility of the test would rely on the timing since the last meal. In pregnancy, plasma glucose concentrations after GCT were higher if administered in the fasting state compared with the postprandial state, and this effect might alter the test characteristics.[22] Therefore, it is important to be cautious in using GCT for diagnostic purposes.

Accuracy is measured by the area under the ROC curve, which summarizes the discriminative ability of a test and provides a measure of the overall performance of a diagnostic test. The greater the value of AUC, the

Table 3. Rate of GDM and GDM + GIGT diagnosed according to GCT results using NDDG criteria and Carpenter and Coustan criteria in patients ≥35 years.

National Diabetes Data Group									
		GDM					**GDM+GIGT**		
		+	-	**Total**			+	-	**Total**
GCT	≥220	12 (100%)	0	12	**GCT**	≥220	12 (100%)	0	12
	<220	73 (42.3%)	99 (57.7%)	172		<220	111(64.5%)	61 (35.5%)	172
	Total	85 (46.1%)	99 (53.9%)	184		Total	123 (66.8%)	61 (33.2%)	184
Carpenter and Coustan criteria									
		GDM					**GDM+GIGT**		
		+	-	**Total**			+	-	**Total**
GCT	≥220	12 (100%)	0	12	**GCT**	≥200	32 (100%)	0	32
	<220	94 (54.6)	82 (45.4%)	172		<200	128 (84.2%)	24 (15.8)	152
	Total	106 (57.2%)	82 (42.8%)	184		Total	160 (87.8%)	24 (12.2%)	184

GDM: Gestational diabetes mellitus; GIGT: Gestational impaired glucose intolerance.

better would be the test.[23] In this study, for GCT values ≥180 mg/dL, we generated ROC curves and calculated AUC. The best value was 0.680 in the curve of GDM + GIGT diagnoses using CC criteria, which provided low accuracy. This is the first study analyzing PPVs of GCT results for diagnosing both GDM and GIGT. Although, women with one elevated glucose tolerance test value are not diagnosed with GDM, they may still be at risk of adverse perinatal outcomes, and dietary counseling and glucose monitoring is recommended to decrease perinatal morbidity.[24] Women with one elevated glucose tolerance test value have an increased likelihood of developing an abnormal glucose tolerance later in life, which is similar to the risk in women with gestational diabetes.[25] Since most clinicians offer glucose monitoring for GIGT, we analyzed the predictive value of GCT results for diagnosing GDM and both GDM and GIGT.

The major limitation of our study is its retrospective design, but it would be difficult to include a large cohort in a prospective study. We could not analyze the effect of other risk factors like maternal weight, positive family history of diabetes, and personal history of previous gestation diabetes. Also, we did not assess the reproducibility of GCT results and obstetric outcomes. However, we focused on the impact of age for the diagnostic utility of GCT results for diagnosing GDM and GIGT. Our data suggest that we may omit OGTT in pregnant women with GCT results ≥230 mg/dL. A cutoff value of 200 mg/dL can be used in patients older than 35 years. This approach may prevent overdiagnosis, and unnecessary interventions can be avoided.

Table 4. Receiver-operator characteristic curve analysis of GCT results ≥180 mg/dL for diagnosing GDM and GDM + GIGT using NDDG and CC criteria in patients ≥35 years.

Criteria	Diagnosis	AUC	95% CI	*P* value
NDDG	GDM	0.599	0.509-0.690	.0293*
	GDM + GIGT	0.629	0.544-0.713	.0070
CC	GDM	0.597	0.511-0.684	.0331*
	GDM + GIGT	0.630	0.542-0.718	.0127

GCT: Glucose challange test; GDM: gestational diabetes mellitus; GIGT: gestational impaired glucose intolerance; NDDG: National Diabetes Data Group; CC: Carpenter and Coustan; AUC: area under curve; CI: confidence interval.

*Not significant because of Bonferrroni corrections.

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Health-related quality of life of Saudi hepatitis B and C patients

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BACKGROUND AND OBJECTIVES: Although usually asymptomatic, many chronic hepatitis C patients have extrahepatic manifestations and impaired health-related quality of life (HRQOL), while hepatitis B virus (HBV) patients have normal or nearly normal HRQOL. The aim of this study was to investigate HRQOL in Saudi patients infected with hepatitis C virus (HCV) in comparison with patients infected with HBV in an effort to document the prevalence of and find factors associated with reduced HRQOL in these patients.

DESIGN AND SETTING: A prospective study that enrolled patients attending a tertiary care referral hepatology clinic in Riyadh from the period of February to July 2008.

PATIENTS AND METHODS: Consecutive patients who had a confirmed diagnosis of hepatitis C or hepatitis B were asked to fill out the SF-36 questionnaire. Information on epidemiological, educational, economic, and social parameters was collected. All clinical, laboratory, and available histological data were recorded.

RESULTS: Two hundred and twenty patients (107 with hepatitis B and 113 with hepatitis C) satisfied the inclusion criteria and participated in this study. Overall, 45% were men, and the average age was 41.6 (18.1) years. Patients with HCV had significantly lower scores in "physical functioning," "role limitations due to physical functioning," "social functioning," and "bodily pain." No significant differences in other parameters were observed. Various epidemiological and laboratory parameters were correlated with different HRQOL domains.

CONCLUSIONS: Saudi hepatitis C patients showed significantly lower HRQOL scores in various domains compared to hepatitis B patients.

Health-related quality of life (HRQOL) has recently become an important outcome in clinical research.[1] In addition to clinical and economic data, it has proven helpful in managing patients better and providing information to health care decision makers. Although it is hard to accurately define "quality of life,", the term "health-related quality of life" focuses on self-perceived health and the general well-being domains of physical functioning, somatic sensations, physiological status, social interactions, functional capacity, and sense of well-being as influenced by health status.[2]

Although the majority of chronic hepatitis C patients are asymptomatic, many extrahepatic manifestations, such as fatigue, anorexia, myalgia, arthralgia, irritability and headaches, can lead to impaired HRQOL.[3] On the other hand, there have been few studies on hepatitis B patients, and those that have been done suggest a normal or nearly normal HRQOL in patients infected with hepatitis B virus (HBV).[4-6] This has led to the assumption that in addition to the virus, many other factors are probably associated with the poor quality of life of patients with hepatitis C virus (HCV), including a number of physical and psychological factors.[7,8]

Viral hepatitis is an important medical problem in Saudi Arabia. Although important research has been performed in relation to this problem in terms of epidemiological prevalence, natural history, and antiviral therapy, no study has addressed the HRQOL issues in these patients. The aim of this study was to investigate HRQOL in Saudi patients infected with HCV in comparison with patients infected with HBV in an effort to document the prevalence of and find factors associated with reduced HRQOL in these patients.

PATIENTS AND METHODS

Consecutive patients attending the hepatology clinic at King Khalid University Hospital in Riyadh between

February and July 2008 were approached for participation in this study. Inclusion criteria were age above 18 and a positive anti-HCV antibody test with confirmation by HCV RNA polymerase chain reaction or positive hepatitis B surface antigen. Exclusion criteria were inability to give informed consent, clinical evidence of decompensated liver cirrhosis (ascites, history of hepatic encephalopathy, or history of variceal bleeding), a history of intravenous drug use, current alcohol or drug abuse, concomitant significant medical illness (such as chronic renal failure, heart failure, or chronic lung disease), well-known diagnosed significant psychiatric illness, and current use of antiviral therapy. The study was explained to all patients, and each signed an informed consent form. The SF-36 questionnaire was fully explained to each patient, and then the forms were filled out by patients themselves. The previously validated Arabic version of the SF-36 questionnaire was used. Patients were also asked to fill out a questionnaire that contained additional personal information on marital status, number of family members, educational level, average income, and living conditions. The patients' charts were accessed, and other general medical information was recorded. The study was approved by the institutional review board of the College of Medicine at King Saud University.

Table 1. Demographics of the study population.

	Total (N=220)	HCV patients (n=113)	HBV patients (n=107)	*P*
Age	41.6 (18.1)	45.7 (18.6)	37.3 (16.6)	.0005
Gender				
Male	100 (45.5)	36 (31.9)	64 (59.8)	<.0001
Female	120 (54.6)	77 (68.1)	43 (40.2)	
Marital status				
Married	203 (92.3)	104 (82.0)	99 (92.5)	.45
Single	12 (5.5)	5 (4.4)	7 (6.5)	
Divorced	2 (0.9)	2 (1.8)	0	
Widowed	3 (1.4)	2 (18)	1 (0.9)	
Children				
No	162 (73.6)	78 (69.0)	84 (78.5)	.11
Yes	90 (26.4)	35 (31.0)	23 (21.5)	
Level of education				
No high school	123 (55.9)	75 (66.4)	48 (44.9)	.002
High school	41 (18.6)	19 (16.8)	22 (20.6)	
College	48 (21.8)	14 (12.4)	34 (31.8)	
Postgraduate	8 (3.6)	5 (4.4)	3 (2.8)	
Employment status				
Unemployed	185 (84.1)	98 (86.7)	87 (81.3)	.54
Temporarily unemployed	2 (0.9)	1 (0.9)	1 (0.9)	
Employed	33 (15.0)	14 (12.4)	19 (17.8)	
Personal yearly income ($)				
<20 000	177 (80.5)	90 (79.7)	87 (81.3)	.26
20 000–50 000	24 (10.9)	15 (13.3)	9 (8.4)	
50 000–80 000	15 (6.8)	5 (4.4)	10 (9.4)	
>80 000	4 (1.8)	3 (2.7)	1 (0.9)	

HCV: Hepatitis C virus; HBV: hepatitis B virus. Values expressed as mean (standard deviation) or frequency (percentage).

Data was entered into an MS Excel spreadsheet. Individual HRQOL items were re-coded, summed, and transformed according to the standardized formula. Descriptive statistics were summarized as a mean score and standard deviation (SD) and median (range) as appropriate. The chi-square test was used to examine relations between categorical variables. Comparison of continuous variables was done using the *t* test or the Wilcoxon-Mann-Whitney test for skewed data. The correlation between continuous variables was evaluated by calculating the Pearson correlation coefficient (r), with skewed data being logarithmically transformed first. The backward stepwise multiple linear regression was used to assess predictors of SF-36 parameters. Variables were retained in the final models if they were significantly associated with the SF-36 parameter being tested. A *P* value of .05 was considered as statistically significant. All analyses were performed with Stata Version 10 (Stata Corporation, College Station, TX, USA).

RESULTS

Two hundred and twenty patients (107 with hepatitis B and 113 with hepatitis C) satisfied the inclusion criteria and participated in this study. Overall, 45% were men, and the mean (standard deviation) of age was 41.6 (18.1) years (Demographic characteristics are shown in **Table 1**). There was a significant difference between HBV- and HCV-infected patients in terms of age (patients with HBV were significantly older, *P*<.0001) and level of education (P=.002). No significant differences were observed between HBV- and HCV-infected patients in terms of other medical characteristics (summarized in **Table 2**). Only 27% of the study population had undergone a liver biopsy. Among these, the majority had grades 0 to 2 (62.3%) and stages 0 to 2 (57.5%). More patients infected with HCV than with HBV underwent a liver biopsy. More patients in the HCV group than in the HBV group had stage 3 or 4 fibrosis, though this did not reach statistical significance. Patients with HCV also had significantly higher alanine aminotransferase (ALT, *P*=.0005), aspartate aminotransferase (AST, *P*=.0003), and alkaline phosphotase (ALP, *P*=.03) levels. Albumin, international normalized ratio (INR), and bilirubin did not show significant differences (**Table 2**).

When patients with HCV and HBV were compared in terms of the SF-36 results, patients with HCV had significantly lower scores in physical functioning (PF), role limitations due to physical functioning (RP), social functioning (SF), and bodily pain (BP) (**Table 3**). No significant differences were observed in other parameters: role limitations due to emotional problems (RE), energy/fatigue (E/F), emotional well-being (EW), and general health (GH).

Several demographic factors were studied to see if there were any correlations with SF-36 scores. Age was associated with reduced SF-36 scores in the following domains: PF (P=.0002), RP (P=.0002), E/F (P=.02), and BP (P=.001). Female gender was associated with a low score in the following areas: PF (P=.001), RP (P=.0009), E/F (P=.001), and BP (P=.004). Increasing level of education was associated with higher scores in PF (P<.0001), RP (P<.0001), E/F (P=.0004), and BP (P=.0009). Employment was associated with a higher score in PF (P=.03) only. There were no associations with marital status, number of children, or income.

Various laboratory parameters weere studied to determine if they correlated with SF-36 scores (**Tables 4 and 5**). Overall, albumin correlated with PF (r=0.24, P=.0004), RP (r=0.20, P=.003), E/F (r=0.18, P=.008), EW (r=0.14, P=.04), SF (r=0.14, P=.04), BP (r=0.22, P=.001), and GH (r=0.17, P=.01). LogAST correlated with E/F (r=−0.19, P=.005), SF (r=−0.22, P=.001), BP (r=−0.25, P=.0003), and GH (r=−0.19, P=.006). Bilirubin only correlated with SF (r=−0.14, P=.04). In HCV patients, albumin correlated with E/F (r=0.21, P=.03), and EW (r=0.21, P=.03), whereas INR correlated with SF (r=−0.21, P=.03) and GH (r=−0.20, P=.03), and logAST correlated with E/F (r=−0.24, P=.01) and EW (r=−0.24, P=.01) (**Table 4**). In patients with HBV, albumin correlated with PF (r=0.32, P=.0006), RP (r=0.24, P=.01), SF (r=0.19, P=.04), BP (r=0.30, P=.002), and GH (r=0.21, P=.03), whereas INR correlated with SF (r=−0.23, P=.02) and GH (r=−0.19, P=.04), and logAST correlated with SF (r=−0.24, P=.02), BP (r=−0.31, P=.001), and GH (r=−0.29, P=.003) (**Table 5**).

In multivariate analyses, several factors predicted different SF-36 domains, as summarized in **Table 6**. LogAST was the most common independent variable negatively associated with several SF-36 parameters including PF, RP, E/F, SF and GH in patients with HBV and EF in patients with HCV. Education and female gender were the next most common predictors of SF-36 parameters. In general, high school graduates were more likely to report lower SF-36 scores particularly in the domain of PF, RP, E/F, and BP in HCV patients and PF, RP and EW in patients with HBV. Only in patients with HBV did female gender appear to be a strong negative predictive factor of SF-36 parameters such as PF, RP, RE, E/F and EW.

Table 2. Medical characteristics of the study population.

	Total (N=220)	HCV patients (n=113)	HBV patients (n=107)	*P*
History of previous treatment				
No	213 (96.8)	111 (98.2)	102 (95.3)	.22
Yes	7 (3.2)	2 (1.8)	5 (4.7)	
Other medical illness				
No	203 (92.3)	102 (90.3)	101 (94.4)	.25
Yes	17 (7.7)	11 (9.7)	6 (5.6)	
History of psychiatric illness				
No	214 (97.3)	111 (98.2)	103 (96.3)	.37
Yes	6 (2.7)	2 (1.8)	4 (3.7)	
Liver biopsy				
No	157 (71.4)	71 (62.8)	86 (80.4)	.004
Yes	63 (28.6)	42 (37.2)	21 (19.6)	
Grade				
0	0	0	0	.18
1	13 (21.3)	6 (14.6)	7 (35.0)	
2	25 (41.0)	17 (41.5)	8 (40.0)	
3	19 (31.2)	14 (34.2)	5 (25.0)	
4	4 (6.6)	4 (9.8)	0	
Stage				
0	2 (3.3)	1 (2.4)	1 (5.0)	.18
1	14 (23.0)	6 (14.6)	8 (40.0)	
2	19 (31.2)	13 (31.7)	6 (30.0)	
3	21 (34.4)	17 (41.5)	4 (20.0)	
4	5 (8.2)	4 (9.8)	1 (5.0)	
ALT (U/L)	60 (17-459)	83 (15-784)	50 (17-460)	.005
AST (U/L)	35 (11-257)	47 (11-197)	29.5 (11-257)	.0003
ALP (U/L)	98.5 (42-550)	103 (44-550)	90 (42-260)	.03
Albumin	37.3 (7.0)	37.1 (7.1)	37.6 (6.9)	.63
INR	1.1 (0.2)	1.1 (0.2)	1.2 (0.3)	.07
Bilirubin	10 (0.7-121)	10 (3-65)	10 (0.7-121)	.74

HCV: Hepatitis C virus; HBV: hepatitis B virus; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphotase; INR: international normalized ratio. Values expressed as median (range) or mean (standard deviation) or frequency (percentage) otherwise.

DISCUSSION

Many studies have shown that HCV may compromise HRQOL.[9] For example, in 642 HCV-infected patients studied before and after treatment with interferon-based antiviral therapy, there was a significant reduction in HRQOL at presentation in patients with HCV compared with healthy controls in the pres-

Table 3. SF-36 scores by hepatitis status.

	Total (N = 220)	HCV patients (n=113)	HBV patients (n=107)	*P*
Physical functioning	66.8 (28.7)	60.0 (28.7)	73.8 (27.2)	.0003
Role limitations because of physical functioning	58.6 (41.7)	50.0 (40.8)	67.8 (40.9)	.002
Role limitations because of emotional problems	62.1 (42.7)	63.4 (42.0)	60.7 (43.6)	.64
Energy/Fatigue	55.4 (20.6)	52.8 (21.7)	58.1 (19.2)	.06
Emotional well-being	68.1 (19.4)	68.8 (20.2)	67.4 (18.6)	.59
Social functioning	78.3 (26.5)	74.1 (28.9)	82.7 (23.0)	.02
Bodily pain	71.9 (29.1)	67.1 (30.7)	76.9 (26.5)	.01
General health	60.5 (19.2)	59.6 (20.1)	61.4 (18.3)	.49

Values expressed as mean (standard deviation).

Table 4. Relationship between SF-36 scores and laboratory results in HCV patients (expressed as the Pearson r).

	Log ALT	Log AST	Log ALP	Albumin	INR	Log bilirubin
Physical functioning	-0.00 (.99)	-0.071 (.47)	-0.03 (.79)	0.16 (.09)	0.03 (.79)	0.13 (.18)
Role limitations because of physical functioning	0.09 (.32)	-0.03 (.76)	-0.11 (.23)	0.16 (.09)	0.02 (.80)	0.10 (.30)
Role limitations because of emotional problems	0.09 (.36)	-0.03 (.79)	-0.09 (.37)	0.10 (.28)	-0.09 (.37)	0.11 (.23)
Energy/Fatigue	-0.13 (.17)	-0.24 (.01)	-0.18 (.06)	0.21 (.03)	-0.02 (.86)	-0.03 (.74)
Emotional well being	-0.13 (.17)	-0.24 (.01)	-0.18 (.06)	0.21 (.03)	-0.02 (.86)	-0.03 (.74)
Social functioning	-0.08 (.37)	-0.15 (.11)	-0.07 (.45)	0.09 (.35)	-0.21 (.03)	-0.14 (.14)
Bodily pain	-0.02 (.81)	-0.14 (.16)	-0.18 (.05)	0.15 (.12)	-0.05 (.61)	0.007 (.94)
General health	-0.03 (.75)	-0.09 (.34	-0.03 (.75)	0.13 (.18)	-0.20 (.03)	0.002 (.98)

ALT: Alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphotase; INR: international normalized ratio.

ence or absence of cirrhosis.[10] In another study by the International Hepatitis Interventional Therapy Group, Ware et al reported that 5 out of 8 SF-36 domains, physical functioning, role-physical, general health, vitality, and social functioning, were significantly reduced in patients with HCV compared with matched population controls.[11]

However, it is important to note that not all studies on patients with HCV have shown these results. In one study, American blood donors who had been found by chance to have HCV (who seemed to have a high incidence of fatigue [61%] and headache [54%]) in a previous study were re-examined in comparison to normal healthy blood donors without HCV. The fatigue rate in the non-HCV group was as high as 70%, suggesting no difference between the two groups.[12] The situation is less clear in terms of HBV, as only a few studies were available on HRQOL in this group of patients. In a study from Britain, 72 unselected, sequential patients with chronic HCV infection were compared with 30 sequential patients with chronic HBV infection with hepatitis B e antigen positivity.[4] All of the SF-36 scores were markedly reduced in patients with chronic HCV infection, whereas in patients with chronic HBV in-

Table 5. Relationship between SF-36 scores and laboratory results in HBV patients (expressed as Pearson r).

	Log ALT	Log AST	Log ALP	Albumin	INR	Log bilirubin
Physical functioning	0.06 (.56)	-0.08 (.41)	-0.11 (.25)	0.32 (.0006)	-0.02 (.85)	0.04 (.67)
Role limitations because of physical functioning	0.02 (.81)	-0.12 (.24)	-0.12 (.20)	0.24 (.01)	-0.05 (.61)	-0.10 (.31)
Role limitations because of emotional problems	0.06 (.54)	0.02 (.83)	-0.08 (.43)	0.12 (.21)	-0.05 (.62)	-0.007 (.94)
Energy/Fatigue	0.003 (.98)	-0.10 (.33)	-0.15 (.12)	0.14 (.15)	-0.06 (.51)	-0.05 (.59)
Emotional well-being	0.14 (.14)	0.06 (.52)	-0.04 (.65)	0.19 (.05)	0.04 (.70)	0.20 (.04)
Social functioning	-0.08 (.42)	-0.24 (.02)	-0.19 (.05)	0.19 (.04)	-0.23 (.02)[a]	-0.17 (.08)
Bodily pain	-0.09 (.36)	-0.31 (.001)	-0.20 (.04)	0.30 (.002)	-0.18 (.06)	-0.18 (.06)
General health	-0.04 (.67)	-0.29 (.003)	-0.22 (.02)	0.21 (.03)	-0.19 (.04)	-0.25 (.01)

HBV: Hepatitis B virus; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphotase; INR: international normalized ratio

Table 6. SF-36 scores and multivariate analysis.

	HCV patients			HBV patients		
SF-36 score		**Regression coefficient (CI)**	***P***		**Regression coefficient (CI)**	***P***
Physical functioning	High school College Postgraduate	10.3 (-3.8, 24.3) 19.5 (3.5, 35.5) 32.5 (7.2, 57.8)	0.15 0.02 0.01	Gender (female) High school College Postgraduate Log AST	-21.0 (-30.5, -11.5) 4.3 (-7.7, 16.3) 18.1 (7.7, 28.4) 27.1 (-0.003, 54.1) -7.5 (-14.5,-0.6)	<.0001 .48 .001 .05 .03
Role limitations because of physical functioning	High school College Postgraduate	9.6 (-10.4, 29.8) 30.2 (7.4, 53.0) 37 (0.8, 73.2)	0.35 0.01 0.04	Gender (female) High school College Postgraduate Log AST	-25.1 (-40.6, -9.7) 8.0 (-10.4, 29.8) 22.8 (7.4, 53.0) 40.7 (0.8, 73.2) -12.6 (-23.9, -1.3)	.02 .42 .009 .07 .03
Role limitations because of emotional problems	-		-	Gender (female)	-18.6 (-35.4, -1.9)	.03
Energy/Fatigue	High school College Postgraduate Log AST	7.4 (-3.3, 18.1) 13.4 (1.3, 25.4) 12.7 (-6.3, 31.8) -8.0 (-14.3, -1.8)	0.17 0.03 0.19 0.01	Gender (female) Log AST	-14.2 (-21.3, -7.1) -5.2 (-10.5, 0.03)	<.0001 .04
Emotional well-being	-		-	Gender (female) High school College Postgraduate	-13.1 (-19.8, -6.4) 2.7 (-6.0, 11.4) 8.5 (0.88, 16.1) 26.4 (6.7, 46.0)	<.0001 .54 .03 .009
Social functioning	INR	-10.9 (-20.5, -1.3)	0.03	Log AST	-7.9 (-14.3, 1.5)	.02
Bodily pain	High school College Postgraduate	18.2 (3.2, 33.3) 21.5 (4.4, 38.6) 21.0 (-6.0, 48.1)	0.02 0.01 0.13	Albumin	1.2 (0.5, 1.9)	.002
General health	INR	-7.3 (-14.0, -0.54)	0.04	Log ALT Log AST	10.4 (2.9, 17.9) -16.0 (-23.7, -8.3)	.007 <.0001

CI: Confidence interval; HCV: Hepatitis C virus; HBV: Hepatitis B virus; ALT: alanine aminotransferase; AST: aspartate aminotransferase;

fection, no significant reductions in the SF-36 scores were observed except in the variables of "mental health" and "general health perception." When the two groups (HCV and HBV) were compared directly, patients with HCV had more impairment in social functioning, physical limitations, and energy and fatigue parameters compared to patients with HBV. Similar results were found in another study where patients with HCV were compared with patients with HBV and primary biliary cirrhosis (PBC) as well as healthy controls.[5] Both patients with HCV and PBC had significantly lower HRQOL scores, whereas patients with HBV had similar HRQOL scores as healthy controls. This has been confirmed in a more recent study from Asia, in which HRQOL scores in HBV inactive carriers were found to be similar to those of healthy controls, but slightly higher than in patients with active HBV infection.[6]

Although the above studies suggest that chronic HCV, but not HBV appears to directly compromise HRQOL, multiple factors related to personality, upbringing, and ethnic background may affect the frequency of reporting of HRQOL parameters. This has led to different prevalence rates of reduced HRQOL scores when HCV-infected patients have been studied in different ethnic backgrounds. For example, in a study by a Japanese group, no characteristic subjective symptoms in patients with HCV compared to healthy controls were found, except for a lower aggression score.[13] This was confirmed by another study from Japan.[14] Similarly, in an interesting study from Egypt, where patients were tested for HRQOL before knowing their HCV status, 146 HCV-positive patients had similar scores, compared to 1140 uninfected controls from the same rural area.[15] This interesting result has been explained by a possibly lower morbidity among Egyptian HCV-infected patients, by a higher morbidity among uninfected controls, or by the effect of not knowing the diagnosis at the time of testing.

This variation in the published studies and the likely effects of non-viral factors in HRQOL in viral hepatitis patients have led us to study the changes in HRQOL in Saudi Arabian patients. Unlike the majority of patients in the Western countries, most patients infected with HCV in Saudi Arabia are not intravenous drug users and have been infected through blood transfusion or unknown causes mostly thought to be iatrogenic. In the current study, significant differences were observed between Saudi patients with HCV and HBV in 4 out of 8 domains of the SF-36 questionnaire. When laboratory parameters showed significant correlations with SF-36 domains, most of these laboratory parameters were related to liver function (albumin, INR, and AST), suggesting that active liver disease or perhaps significant fibrosis was more likely affecting the HRQOL domain score rather than the virus itself. Although the stage and grade of inflammation of liver biopsy did not confirm this assumption, it has to be remembered that only 27% of the study population had had a liver biopsy. The results from our multivariate analysis show that the AST level is associated with the quality of life in patients with HCV, further supporting that active disease has an impact on the quality of life in these patients. The general trend of patients with lower educational status reporting lower scores could be because these patients have limited understanding of HCV and HBV, which may in turn lead to poorer disease management. As Saudi Arabia has an equal-access health care system, it is unlikely that inadequate access to health care is a reason for this disparity.

Like any other study, this study has some strengths and suffers from some limitations. In terms of strengths, to our knowledge, it is the first to study HRQOL in viral hepatitis patients in Saudi Arabia and is among only a few in the Arab world. It is also among the few studies worldwide that have compared patients with HCV and HBV directly. Similarly, it is one of few studies to correlate HRQOL measures with biochemical parameters. One limitation of this study is that the SF-36 scores were not compared to expected Saudi Arabian norms, as such data have not been produced. Both HCV and HBV groups served as controls for one another. Second, the percentage of patients who had had a liver biopsy in this study was low, making us unable to clearly understand the positive correlation between the reduced HRQOL scores and the levels of albumin, INR, and AST. Although none of these patients had clinical evidence of decompensated liver disease, some did have histologically (subclinical) advanced fibrosis, which might have affected their HRQOL. Third, all patients included in this study were patients who were seen in a tertiary care center, which may not represent the majority of the HCV patient pool.[16] This fact is important, as knowledge of the diagnosis and the psychological stress related to medical care may significantly influence HRQOL. Two interesting studies examined patients presenting with chronic fatigue syndrome and assessed their HCV status retrospectively to avoid the psychological effects of knowing about the HCV infection.[17,18] Neither study reported an association between HCV status and chronic fatigue. Similarly, in the aforementioned study in rural Egypt, patients who were not aware of their viral status also showed no significant reduction in HRQOL compared to the general population.[15] Fourth, we used only one HRQOL instrument. Although SF-36 is the most reliable and widely used tool, it can be argued that a more sensitive tool would have been needed to detect very subtle changes, especially in patients with HBV. In conclusion, our sample of Saudi hepatitis C patients show significantly lower HRQOL scores in various domains compared to hepatitis B patients.

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original article

Pattern of patch test reactivity among patients with clinical diagnosis of contact dermatitis: a hospital-based study

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BACKGROUND AND OBJECTIVES: Contact allergy is associated with a significant morbidity all over the world. This study was performed to investigate the pattern of sensitization by contact allergens in the local population.
DESIGN AND SETTING: Retrospective study to investigate patch test reactivity among patients with clinical diagnosis of contact dermatitis who were referred to the allergy clinic at the King Khalid University Hospital, Riyadh, between April 2008 and March 2010.
PATIENTS AND METHODS: Of the 196 patients referred to the allergy clinic over the 2-year period, 91 (46.4%) patients reacted to one or more patch test allergens, and these patients were included in this study. The study group included 82 (91.1%) of Saudi nationality and 9 (8.9%) patients of other nationalities. The patch test was performed using the T.R.U.E TEST, containing 24 allergens/allergen mixes.
RESULTS: Of the 91 cases who reacted positively to one or more allergens, 67 (73.6%) were females with a mean age of 37 (8.3 years) and 24 (26.4%) were males with a mean age of 34 (11.6 years). Thirty-three (36.2%) patients reacted to nickel sulfate, 14 (15.3%) to *p*-phenylenediamine, 13 (14.2%) to *p*-tert-butylphenol-formaldehyde resin, 13 (14.2%) to thimerosal, and 9 (9.8%) to colophony. Reactivity against the rest of the allergens was not remarkable. A significantly higher percentage of females reacted to nickel sulfate (84.8% vs 15.2% in males; *P*=.0001), p-tert-butylphenol-formaldehyde resin (92.3% vs 7.7%; *P*=.0001), and thimerosal (76.9% vs 23.1%; *P*=.03).
CONCLUSIONS: Patch test reactivity to nickel sulfate was high. The pattern of contact allergy observed in this study indicates the need for large-scale investigations to identify local allergens responsible for contact allergy and for formulation of policies directed towards avoidance of exposure.

Contact dermatitis (CD) is a common clinical condition affecting the skin. Most commonly it is caused by irritants and only a relatively small proportion is due to allergy. Allergic contact dermatitis (ACD) frequently involves the hands and face.[1] During the acute phase the most common symptom is itching, which may be associated with vesicle and bullae formation. Scaling and lichenification are features of chronic ACD.[2] As opposed to irritant contact dermatitis (ICD), ACD is believed to be an immunological reaction and requires prior allergen sensitization.[3] However, there is evidence indicating that the immune system plays a significant role in the pathogenesis of ICD as well.[4] ICD is thought to be a non-antigen-specific inflammatory process mediated by haptens[5] and associated with release of cytokines and recruitment of dendritic cells.[6,7] Hapten-induced ICD is thought to evolve into ACD by acquisition of antigenic properties by haptens subsequent to their binding and modification of self-proteins.[8] Recently it has been suggested that ICD and ACD are closely associated, and the induction of ICD may be a prerequisite for the development of ACD.[9]

ACD comprises about 6% to 10% of all dermatology clinic visits and is associated with significant morbidity.[10] Allergen sensitization is believed to be dependent on the degree of exposure to the allergen and exhibits strong individual variation. Genetic predisposition appears to be an important factor, as some individuals are more easily sensitized to common allergens than others.[11] In addition, regional and environmental factors may also influence the exposure patterns and could be responsible for the variations in the patterns of skin reactivity observed in different parts the world.[12,13]

The patch test is a useful tool for the detection and identification of contact allergens, despite the fact that 10% to 15% of normal healthy individuals may react to one or more allergens.[14,15] In patients with ACD, detection of the relevant agent by patch testing is crucial for instituting appropriate prevention and treatment.[16] Avoidance of the relevant allergen/s has recently been shown to be associated with significant improvement in over 85% of patients with ACD.[17] Over 3000 chemicals are known to cause ACD but, fortunately, only a small number of these chemicals are responsible for symptoms in the majority of cases.[18] Thorough knowledge of the common allergens and a comprehensive history of the patient's exposure to possible allergens will be valuable for selecting the test panels for patch testing. This retrospective study examines patch test reactivity to common allergens in patients with clinical suspicion of CD over a period of 2 years.

PATIENTS AND METHODS

A total of 196 patients with the clinical diagnosis of CD were referred to the allergy clinic at KKU Hospital for patch testing between April 2008 and March 2010. Because of the lack of access to the patient records, clinical data could not be collected.

The patch test was performed using T.R.U.E. Test (Thin-layer Rapid Use Epicutaneous Test, Mekos Laboratories AS, Denmark) with a panel of 24 allergens/allergen mixes. The test panel was applied on the upper part of the patient's back on healthy skin free of acne, scars, dermatitis, or any other skin condition that might interfere with the interpretation of the results. Patients were instructed to wear the patch for 48 hours without removing it and to avoid contact with water. Interpretation of the results was performed first after 48 hours and then again 72 to 96 hours after the application. This protocol allowed sufficient time for the allergic reactions to fully develop and for mild irritant reactions to disappear. Patients were instructed to report back to the clinic in case of delayed reactions. The interpretation of the results was performed in accordance with the recommendations of the International Contact Dermatitis Research Group (ICDRG) and the North American Contact Dermatitis Group (NACDG). Statistical analysis of the data was performed using MedCalc software version 11.5.1.0 for comparison of the proportions. $P\leq.05$ was considered statistically significant.

RESULTS

Out of 196 patients suspected to have CD, 91 (46.4%) individuals tested positive to either one or more allergens; these included 24 males with a mean age of 34 (11.6) years and 67 females with a mean age of 37 (8.3) years. These 91 patients included 82 (91.1%) of Saudi nationality and 9 (8.9%) patients of other nationalities. Among the 91 patients, 56 (61.5%) reacted positively to a single allergen. A female preponderance was evident among the patients with CD, with 67 (73.6%) females compared to 24 (26.4%) males showing positive reaction to either one or more allergens in the patch test panel. **Figure 1** shows the pattern of patch test reactivity among the patients with CD. Nickel sulfate was found to be the most frequently reacting allergen, with 33 (36.2%) patients showing reaction to the allergen. A positive reaction was seen with *p*-phenylenediamine in 14 patients (15.3%), with *p*-tert-butylphenol-formaldehyde resin in 13 patients (14.2%), with thimerosal in 13 patients (14.2%), and with colophony in 9 patients (9.8%). Reactivity against the rest of the panel was not remarkable. **Table 1** shows the gender differences among the patients with CD where notable numbers of patients reacted to patch test allergens. The group of 33 patients reacting positively to nickel sulfate had a significantly higher proportion of females (28/33; 84.8%) than males (5/33; 15.2%) (P=.0001). Although the difference was not as marked as with nickel sulfate, a significantly higher number of females than males reacted to *p*-tert-butylphenol-formaldehyde resin (P=.0001) and thimerosal (P=.03).

DISCUSSION

Nickel sulfate was found to be the most frequently (36.2%) reacting patch test allergen in this study. Similar findings were noted in an earlier study performed among adolescents between the ages of 10 to 19 years where 56% of patients reacted to one or more patch test allergens and among them 31% were found to be allergic to nickel.[19] Patch test reactivity between 13% and 17% has also been reported.[20,21] The NACDG has consistently ranked nickel as the most frequently reacting allergen among positive patch test reactions. Because of the presence of nickel in a large variety of products it is very difficult to avoid contact with nickel and this is probably the main reason for the high incidence of nickel allergy.[22] An increase in patch test reactivity to nickel among patients with CD has also been observed: two separate studies, one performed from 1994 to 1996 and the other from 1998 to 2000, reported nickel reactivity in 14.3% and 16.2% of patients, respectively.[23] Collectively, these data indicate that nickel sulfate is not only a common contact sensitizer but that allergy to nickel is gradually increasing, probably due to the increased exposure to nickel.

A significantly higher proportion of females with CD reacted to nickel in the present study. Women have already been reported to be at a higher risk of acquiring allergy to nickel (20.4% vs 5.8% in men).[20] Differences in exposure have been postulated to be the cause for this disparity. Early skin contact with nickel in earrings or pins have been implicated in the increased skin reactivity to nickel among females.[24] Attempts to decrease exposure to nickel in Denmark by legal restriction on earrings with high nickel content have resulted in 64% reduction in nickel allergy among young girls.[25] It has also recently been reported that nickel regulation in Denmark has not only decreased nickel allergy among young females, it has also reduced the occurrence of new cases.[26] Since 2001, the European Parliament and European Council have also imposed restrictions on the use of objects containing nickel that may cause skin sensitization.[27] Nickel allergy appears to be a major public health problem that requires serious consideration and implementation of policies directed towards reducing skin contact with nickel.

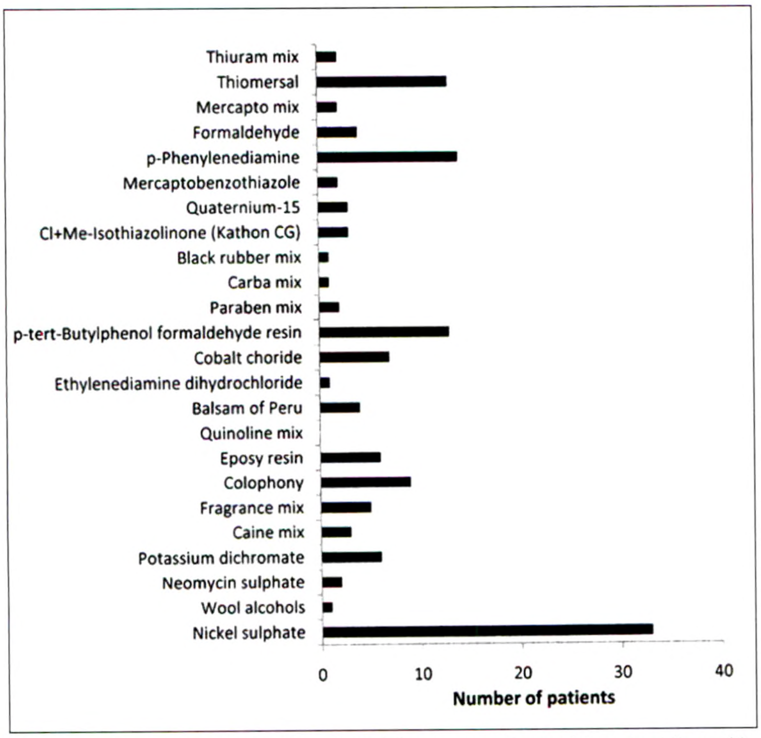

Figure 1. Pattern of allergen patch test reactivity among patients with contact dermatitis (n=91).

Table 1. Gender differences among patients with contact dermatitis in cases where notable patch test allergen reactivity was observed.

Allergen	Number of patients	Number of females (%)	Number of males (%)	*P*
Nickel	33	28 (84.8)	5 (15.2)	.0001
p-Phenylenediamine	14	6 (42.8)	8 (57.2)	Not significant
p-tert-Butylphenol formaldehyde resin	13	12 (92.3)	1 (7.7)	.0001
Thimerosal	13	10 (76.9)	3 (23.1)	0.03
Colophony	09	7 (77.7)	2 (22.3)	Not significant

p-Phenylenediamine (PPD) is commonly used in hair dyes and in Bandrowski base, a trimer that forms quickly upon storage of PPD and is believed to be the main allergen in patients reacting to PPD.[28] A sizeable proportion (15.3%) of patients with CD reacted to PPD in the present study, higher than the proportion (7%) reported in a recent study from Thailand.[29] A significant increase in the skin reactivity to PPD has been observed and this alteration in PPD reactivity has been attributed to the changes in exposure patterns.[30] The use of hair dyes is increasing[31] and, consequently, so is the exposure to PPD, thus accounting for the substantially high prevalence of symptoms such as redness, scaling, itching, or edema following hair dye application.[32] It is therefore imperative to introduce measures to curtail exposure to this sensitizer.

p-tert-Butylphenol-formaldehyde resin is an alkylphenol resin made from p-tert-butylphenol and formaldehyde. It is included in many adhesive formulations. Glues containing *p*-tert-butylphenol-formaldehyde resin are used in leather products such as shoes, watchstraps, handbags, building materials, motorcars, and electrical products.[33] Positive patch test reactions to *p*-tert-butylphenol-formaldehyde resin were detected in 14.2% of the patients with CD in the present study, and reactivity was more frequently seen among females. This appears to be a significantly high percentage when compared to the previous reports that have documented reactivity to *p*-tert-butylphenol-formaldehyde resin of 2.3% in 1984, 1.7% in 1996,[34] and 2.2% in 2000.[35]

Thimerosal patch test reactivity observed in the present study was 14.2%, which was also higher than the recently reported figures of 6.4%[36] in adults and 1.7% in children.[37] Thimerosal has for long been used as a preservative in medical preparations and vaccines.

Its use in vaccines was abandoned in the United States due to public concern.[38]

Although the present study examined a relatively small number of patients with CD, comprised predominantly of Saudi nationality, it does however reveal a pattern of sensitization by contact allergens that this study population was exposed to. High reactivity to nickel has previously been reported from Saudi Arabia in 1995,[39] though the pattern of allergen reactivity was different to what has been found in the present study. Large-scale studies are needed to further investigate the local allergens responsible for CD in Saudi Arabia, which will aid implementation of appropriate measures for avoidance of exposure.

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original article

Puberty development among children and adolescents with chronic disease in Saudi Arabia

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BACKGROUND AND OBJECTIVES: Increasing numbers of children with chronic health conditions are now surviving into adolescence and adulthood because of advancing health care. These chronic health conditions are generally known to impact a child's growth and development, including pubertal development. In Saudi Arabia, chronic diseases are prevalent, yet no reports of pubertal onset and its relation to chronic illness are available. The aim of this study was to explore pubertal development among Saudi children and adolescents with a chronic illness.

DESIGN AND SETTING: Cross-sectional study conducted at schools in Riyadh, Saudi Arabia in 2006.

SUBJECTS AND METHODS: Those students whose parents reported that their son/daughter had a chronic illness and/or was taking a long-term medication underwent a physical examination to determine sexual maturity rating and growth parameters.

RESULTS: Of 1371 students who participated in the study, 155 (11.3%) had a chronic illness. Of those, 79 (51%) were male, and the mean SD age of all the students was 11.4 (2.4) years. Ninety (58%) students were taking medication for their health condition. Bronchial asthma was reported to be the most common chronic condition (n=66; 42.6%), followed by blood disorders (n=41; 26.5%). Fifty-three (34%) students were overweight or obese. For male gonadal (G) development, the mean age of boys with G stage 2 was 11.7 years; stage 3: 13.5 years; stage 4: 14.1 years; and stage 5: 14.6 years. For female breast (B) development, the mean age of girls with B stage 2 was 10.7 years; stage 3: 11.3 years; stage 4: 12.4 years; and stage 5: 14.1 years. The pubic hair development for both boys and girls was similar to the corresponding gonadal or breast development, respectively.

CONCLUSIONS: The age of onset of pubertal development for both boys and girls with a chronic illness are within normal limits. The high prevalence of overweight and obesity may contribute to this phenomenon, yet further studies should consider the effects of disease severity and chronicity and medication use as possible confounders.

With advancing health care, increasing numbers of children with congenital or perinatal health conditions as well as acquired chronic health conditions survive into adolescence and adulthood.[1,2] It has also become common for individuals to suffer from multiple or comorbid chronic conditions.[3] The definition of chronic illness and chronic health conditions has been an area of discussion for many years and includes elements, such as duration of condition, limitations of function, and health care needs.[4,5] An internationally agreed upon definition is essential for research implications and hence different prevalence rates have been reported for children with chronic health conditions or a chronic illness.[2,4,5]

Chronic health conditions come with their own challenges and complications. In addition to the symptoms that present as a result of the condition itself, a child may also experience a negative impact on his/

her physical growth, pubertal development, and overall health-related quality of life.[6-8] Although pubertal delay is a recognized consequence of chronic illness, its incidence is unknown.[7] The hypothalamic-pituitary axis may be affected to varying degrees based on the severity and chronicity of the illness, malnutrition, and long-term use of medications.[6,7,9]

In Saudi Arabia, chronic diseases are prevalent and accounted for 69% of all deaths in 2002.[10] The age of puberty onset among Saudi children has previously been reported to be similar to that in other countries.[11] However, no report is available exploring pubertal onset and development among Saudi children with a chronic illness. The aim of this study was to explore pubertal development among Saudi children and adolescents with a chronic illness.

SUBJECTS AND METHODS

Data for this study was extracted from the Riyadh Puberty Study[11] that was conducted in 2006. This was a cross-sectional study carried out among school children and adolescents in Riyadh, Saudi Arabia. Riyadh is the capital city with over 5 million inhabitants, almost 40% of whom are children and adolescents younger than 15 years of age.[12] Through the cluster sampling strategy, private and public school students were randomly selected to participate in the study. The methods of sampling allowed for representation of different geographical and socioeconomic backgrounds of individuals within the city. The details of sampling technique are described elsewhere.[11] The Institutional Review Board approval was obtained for the study.

Data were collected by means of a household questionnaire as well as a physical examination of the participating student at his/her school. The questionnaire included items pertaining to demographic information, and parents were also asked to identify if their son or daughter was living with a chronic disease and/or taking a medication for a long period. The physical examination included identification of sexual maturity rating (SMR) as well as measurement of growth parameters. SMR for males was determined by assessing gonadal stage and pubic hair development, whereas for females by assessing breast and pubic hair development. Weight and height was measured for all students, with the details of clinical assessment and measurement described elsewhere,[11] and the body mass index (BMI) was calculated. Only students who were not reported to have a chronic illness were included in the analysis of this study. A small number of students were not reported to have a chronic illness, but were taking a long-term medication; hence, they were considered to have a chronic illness.

Descriptive analyses were conducted. Stratified analyses by age for the height, weight, and BMI were also carried out. Moreover, the mean, standard deviation, and 95% confidence intervals of age by stage for pubic hair and gonadal/breast development was calculated. Data management and analyses were carried out using SPSS program (IBM Corp, Armonk, NY, United States, version 15).

RESULTS

Of 1371 students who participated in the study, 155 (11.3%) had a chronic illness. Seventy-nine (51%) of those students were male, and the mean age was 11.4 (2.4) years. The majority of students (92.9%) lived with both of their parents. Ninety (58%) students were taking medication for their health condition.

Chronic diseases were classified into nine disease/system categories: bronchial asthma, allergic disorders (other than bronchial asthma), blood disorders, skin disorders, endocrinopathies, central nervous system and behavioral disorders, musculoskeletal disorders, and genitourinary disorders. All students were reported to have only one single chronic illness, with the most common condition being bronchial asthma (n=66; 42.6%). This was followed by hematological disorders (n=41; 26.5%) and others (**Table 1**).

Table 2 summarizes the mean ages of the stages of pubertal development for both genders.

Seventy-two (46.4%) students had unhealthy weights (BMI was either <5th percentile or more than the 85th percentile for age and gender). Fifty-three (73.6%) of these students with unhealthy weights were either overweight or obese. Out of those students who were found to be underweight (n=19), defined as hav-

Table 1. Distribution of chronic illnesses.

Chronic illness/system involvement	Frequency	%
Allergic disorders (other than asthma)	14	9.0
Asthma	66	42.6
Blood disorders	41	26.5
Central nervous system and behavioral disorders	3	1.9
Endocrinopathies	9	5.8
Genitourinary disorders	5	3.2
Musculoskeletal disorders	5	3.2
Skin disorders	12	7.7
Total	**155**	**100.0**

Table 2. The mean ages of students at the different stages of pubertal development.

Stages	N	Mean	Standard deviation
Males[a] **Gonadal development**			
I	30	9.3	2.0
II	17	11.7	1.3
III	13	13.5	1.5
IV	7	14.1	1.4
V	8	14.6	0.9
Pubic hair			
I	34	9.4	2.0
II	13	11.9	1.2
III	13	13.5	1.5
IV	8	14.1	1.3
V	7	14.7	1.0
Females **Breast development**			
I	23	8.0	0.9
II	9	10.7	1.0
III	9	11.3	0.9
IV	8	12.4	1.9
V	27	14.1	1.9
Pubic hair			
I	32	8.8	1.5
II	5	10.8	0.8
III	7	12.0	0.8
IV	16	12.8	1.8
V	16	15.1	1.5

[a] Four students refused physical examination.

ing a BMI <fifth percentile, thirteen (68.4%) had a blood disorder. The majority of students who were overweight or obese, defined as having BMI between 85th and 95th and >95th percentile, respectively, had bronchial asthma (**Table 3**).

DISCUSSION

The prevalence of chronic illness in Riyadh was found to be similar to that reported in the regional published studies. In Qatif, a city in the Eastern province of Saudi Arabia, the chronic illness was found among 344 respondents (11.7%).[13] International data, such as that from the United States, has shown that the chronic illness is prevalent in 31% of children, and similar to our findings, bronchial asthma is ranked high among the chronic health conditions.[2]

Chronic illness is known to impact pubertal development of both boys and girls and results in delayed onset of pubertal maturation. This obviously depends on the severity of the illness, its degree of chronicity, as well as other factors, including nutritional status and medication use.[6,7,9,14,15] In our study, we found no evidence of delayed puberty. All students exhibited physical evidence of pubertal development within normal limits that was comparable to that of healthy peers.[11] The fact that 53 (34.2%) students were overweight or obese may have played a role in this, as the effect of increased body fatness on triggering the neuroendocrine events of pubertal onset is well documented.[16] Furthermore, no evidence of early onset puberty was available in any of the students, including those who were overweight or obese. This may suggest that the presence of obesity with a coexisting chronic illness may result in a "balance" or equilibrium of the neuroendocrine system and hence result in normal onset of pubertal development.

Interestingly, as mentioned earlier, 53 (34.2%) students were found to be overweight or obese, yet not a single family reported this as being a chronic health condition. Obesity is internationally recognized as being a chronic illness requiring a multidisciplinary team care approach; yet despite this fact, many may not recognize the significance that the increased body mass may have on an individual until specific organ involvement occurs. This is not unusual as it is known that health conditions that impact on a child's functioning and activities or require regular encounters with health care facilities are more accurately reported than conditions that do not.[2] The social and economic consequences that obesity has on young individuals have been reported.[17] Children who have multiple chronic conditions have increased morbidity,[3] and in adults, the presence of obesity in addition to a coexisting chronic illness, as compared to the presence of obesity alone, has been found to affect not only the physical well-being but also the emotional well-being.[18]

Although we had a representative sample of students in Riyadh, the fact that this was a school-based study means that the children and adolescents with a chronic illness impairing their functioning and who may be unable to attend school have not been included. Therefore, we may be reporting an underestimation of the prevalence of chronic disease among school-aged children and adolescents in Riyadh. Overweight and obesity were incidentally found to be highly prevalent, yet parents never reported this as being a chronic illness. This raises the issue of individual understanding and perceptions of chronic illness and health conditions, the possibility of under- or overestimating the existence of such conditions, and the importance of having accurate and internationally accepted definitions or criteria.

In conclusion, the prevalence of chronic disease among children and adolescents in Riyadh is similar to that reported in other parts of the country. It is less prevalent than that reported internationally; however, our report here is probably an underestimation. Bronchial asthma is one of the more prevalent chronic conditions, similar to others' findings. The mean age of pubertal development among students with chronic disease is similar to that of healthy students. The high prevalence of overweight and obesity may be contributing to this phenomenon, yet further studies should consider the effects of disease severity and chronicity and medication use as possible confounders. Because chronic illness has been shown to be prevalent, further studies should explore these individuals' access to health care as well as the impact of such chronic illness on one's well-being, quality of life, and health care costs. Public health education and awareness of the significance of abnormal body mass measures, whether increased or decreased, need to be emphasized.

Table 3. Body mass index according to disease category.

Chronic illness/system involvement	**Body mass index percentiles**				
	<5th	**5–85th**	**>85th–95th**	**>95th**	**Total**
Allergic disorders (other than asthma)	0	8	2	4	14
Asthma	4	32	14	16	66
Blood disorders	13	23	1	4	41
Central nervous system and behavioral disorders	0	1	0	2	3
Endocrinopathies	1	6	0	2	9
Genitourinary disorders	0	2	1	2	5
Musculoskeletal disorders	1	2	1	1	5
Skin disorders	0	9	0	3	12
Total	**19**	**83**	**19**	**34**	**155**

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Current Evidence in Diagnosis and Treatment of Proliferative Verrucous Leukoplakia

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Proliferative verrucous leukoplakia is multifocal and progressive lesion with a high rate of malignant transformation. This short review highlights the diagnosis, traditional treatment and the current management of the disease. A MEDLINE search for the specific English word including proliferative verrucous leukoplakia in the last two years (2009-2010). This study indicates the current evidence for the diagnosis and the management of proliferative verrucous leukoplakia to help the specialist in this domain for early diagnosis of proliferative verrucous leukoplakia according to the new criteria of diagnosis to prevent the recurrence and any malignant transformation.

White lesions are relatively frequent in the oral cavity with a prevalence of approximately 24.8% according to Axéll.[1] Among them is oral leukoplakia with a prevalence 0.2 to 3.6%.[1-5] Leukoplakia was described by the WHO as a "precancerous lesion"[6] and recently this terms was substituted by the terms "Potentially malignant disorders".[7] Its malignant transformation rate varies from 0.1% to 17.5%.[8-10] Proliferative verrucous leukoplakia (PVL) is a distinct clinical form of oral leukoplakia first described in 1985 by Hansen et al.[11] The WHO also described PVL with a high rate of malignant transformation.[12] PVL is multifocal and progressive lesions are seen frequently in women characterized by a recurrence and a high rate of transformation into oral cancer resistant to all forms of treatment.[13]

Proliferative verrucous leukoplakia is more common in elderly women who have had lesions of leukoplakia for many years.[11] Frequently in women and elderly patients over 60 years with a ratio of women/men of 4/1. Smoking and drinking have not been directly associated with PVL.[14]

Clinical characteristics

PVL may appear on any soft tissue of the oral cavity and may be present as single or multifocal growths involving several oral sites. Some have found that the buccal mucosa is the most frequent location in women and the tongue in the men.[15] The area most frequently affected with PVL were the lower gingival, tongue, buccal mucosa, alveolar ridge.[16] Although some research has proposed four stages of development to PVL, which starts as a simple hyperkeratosis without epithelial dysplasia, verrucous hyperplasia, verrucous carcinoma, and conventional carcinoma.[17,18]

Etiopathogenesis and Diagnosis

PVL is of uncertain etiology but may be associated with human papillomavirus (HPV) infection. They suggest that HPV-16 infection may play an important role in theses lesions,[19,20] although some have failed in patients with PVLG to detect HPV-DNA by PCR.[21] It appears that any association between PVL and HPV may be present in some but not all lesions of PVL.[22] The diagnosis of PVL is based on clinical data as a progressive evolution of homogeneous leukoplakia that spreads to different locations with changes in appearance. Histopathology may help to distinct the stage of the disease as described before.

Management

Because of the relentless growth pattern associated with

PVL and its propensity to develop into carcinoma[11,16] early and aggressive treatment of such a lesion is recommended.[15,21] There is no effective management reported. Schoelch et al reported laser treatment using CO_2 and Nd:YAG (neodymium-doped yttrium aluminum garnet), but found a high rate of recurrences of 83%.[23] Bagan et al found a recurrence rate of 86.7% after treatment with CO^2 laser and or/scalpel surgery.[14]

Nonsurgical therapeutic approaches for PVL have been considered such as external beam radiation therapy, cryotherapy, and topical vitamin therapy, but none has proven to be beneficial.[15,18] Early trials of topical chemotherapy with bleomycin have been assessed.[24,25] Surgical shave followed by cryosurgery and photodynamic therapy have also been suggested.[26,27] Antiviral methisoprinol appeared to offer a significant benefit.[28] In the future, anti-HPV, anti-TGF, and pro-apoptotic management strategies may be considered.[29]

Evolution

PVL is an unknown disease in which no etiological factors have been found. The diagnostic criteria are not well established. It is characterized by a high rate of recurrence after treatment and also by malignant transformation in nearly 74% of cases with a tendency for several oral cancer to appear.[30] Bagan et al found recurrences after treatment 86.7% of cases, new lesions during follow up in 83.3%, and oral cancer eventually in 63.3% with a high incidence of the gingival type, which emphasizes the importance of PVL awareness for periodontists.[14]

Saito et al 1999 found that the widespread multiples oral leukoplakias have a higher potential for the development of cancer and probably most of multiple oral leukoplakia develop to PVL.[31]

Ghazali et al[32] establish the following criteria for the diagnostic of PVL:

1) Lesion starts as homogeneous leukoplakia with evidence of dysplasia.
2) With time some areas of the leukoplakia becomes verrucous.
3) Disease progresses to multiple lesions at the same or different site.
4) With time disease progresses into different histological stages.
5) Appearance of new lesion after treatment.
6) Clearly histologically PVL after follow up periods of no less than one year.

On other hand Gandolfo S et al[33] established the following criteria:

1) Homogenous plaque that progresses over time to exophytic, diffuse, multifocal lesions with the verrucous epithelial growth pattern.
2) Histopathologically changes from a simple hyperkeratisis without dysplasia to verrucous hyperplasia, verrucous carcinoma or oral squamous cell carcinoma.

Recently Bagan et al 2010[34] also proposed a set of diagnostic criteria to allow for the early identification of PVL cases. The proposal includes five major criteria and four minor criteria as the following:

Major criteria (MC):

1) A leukoplakia lesion with more than two different oral sites, which is more frequently found in the gingival and alveolar processes and palate.
2) The existence of a verrucous area
3) The lesions spread or become engrossed during development of the disease.
4) Recurrence in a previously treated area.
5) Histopathologically, there can be simple epithelial hyperkeratosis to verrucous hyperplasia, verrucous carcinoma or oral squamous cell carcinoma.

Minor criteria (mc):

1) An oral leukoplakia lesion that occupies at least 3 cm when adding all the affected areas.
2) The patient is female
3) The patient (male or female) is a nonsmoker
4) A disease evolution more than 5 years.

In order to make the diagnosis of PVL, it was suggested that one of the two following combinations of the criteria mentioned before were met: three major criteria (being E among them) or two major criteria (being E among them) + two minor criteria.

Conclusion

PVL is a persistent and progressive oral lesion that require early and aggressive treatment to increase the chances of favorable outcome. Therefore, early diagnosis is recommended as well as consensus on diagnostic criteria, which improves therapeutic approaches.

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Borderline mucinous cystic ovarian tumor with mural nodules (carcinosarcoma)

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Carcinosarcoma mural nodules arising form a mucinous ovarian neoplasm is very rare and only two published cases have been reported. We report a case of a 29-year-old female patient who suffered from severe lower abdominal pain unrelated to menstruation for 1 year. She came to our (Shin-Kong Hospital) gynecology outpatient department in February 2010. The CT scan revealed a large cystic tumor, measuring approximately 36 cm in greatest dimension and at least 2 solid foci were noted. The patient underwent left salpingo-oophorectomy. A carcinosarcoma mural nodule arising within a mucinous ovarian neoplasm was diagnosed. The patient was treated by further chemotherapy and was free of the disease at time of publication. We reviewed the published studies, and in particular looked at the histology and immunohistochemistry of tumors, in which sarcomatoid carcinoma and carcinosarcoma-like nodules were diagnosed. We also discussed the differential diagnosis of the mural nodule in a mucinous cystic neoplasm.

Mucinous cystic tumor with mural nodules is a rare neoplasm; only about 80 cases have been published in the past 30 years.[1] Only two of them had carcinosarcoma in the mural nodules. In these two cases, one was a mucinous cyst adenoma[2] and the other was a mucinous carcinoma.[3] We report a case of a 29-year-old female with a borderline mucinous cystic tumor with mural nodules (carcinosarcoma) (FIGO stage Ia).

CASE

The patient was a 29-year-old nulliparous female and a hepatitis B carrier. She had no operative history and had a normal menstrual cycle. She was unmarried and had no family history of gynecology disease. She did not take any medication in previous years. She suffered had from dysmenorrhea and constipation for years and tolerated it. Lower abdomen swelling was noted for the previous year prior to presentation. She presented with severe lower abdominal pain unrelated to menstruation. She first presented to Shuang-He Hospital and the diagnosis of ovarian tumor was made. The patient came to our (Shin-Kong Hospital) gynecology outpatient department (OPD) for a second opinion in February 2010. At that time, the physical examination was generally normal except for mild tenderness over the lower abdomen with a palpable mass. There was no rebounding pain. The laboratory investigation performed showed an abnormal cancer antigen 125 (CA125) elevated to 55.04 U/mL, CA19-9 elevated to 70.62 U/mL and CA153 elevated to 28.87 U/mL. The carcinoembryonic antigen value and other laboratory data were within normal limits.

The CT scan revealed a large cystic tumor, measuring approximately 36 cm in greatest dimension, with a few thin septa in homogeneous internal attenuation. At least two solid foci were noted and measured approximately 4.5 cm in greatest dimension, attached to the left lateral wall of the tumor (**Figure 1**).

The patient underwent left salpingo-oophorectomy and adhesiolysis. At the time of surgery, a large left ovarian cyst was noted with changes consistent with torsion. The cyst was found to contain a 5400 mL of reddish brown fluid on aspiration. This cystic tumor focally adhered to the peritoneum. The right adnexa were normal on gross examination. The multilocular cystic tumor was received opened in the surgical pathology laboratory. The tumor measured 28×15×3 cm in size and weighed 600 g (**Figure**

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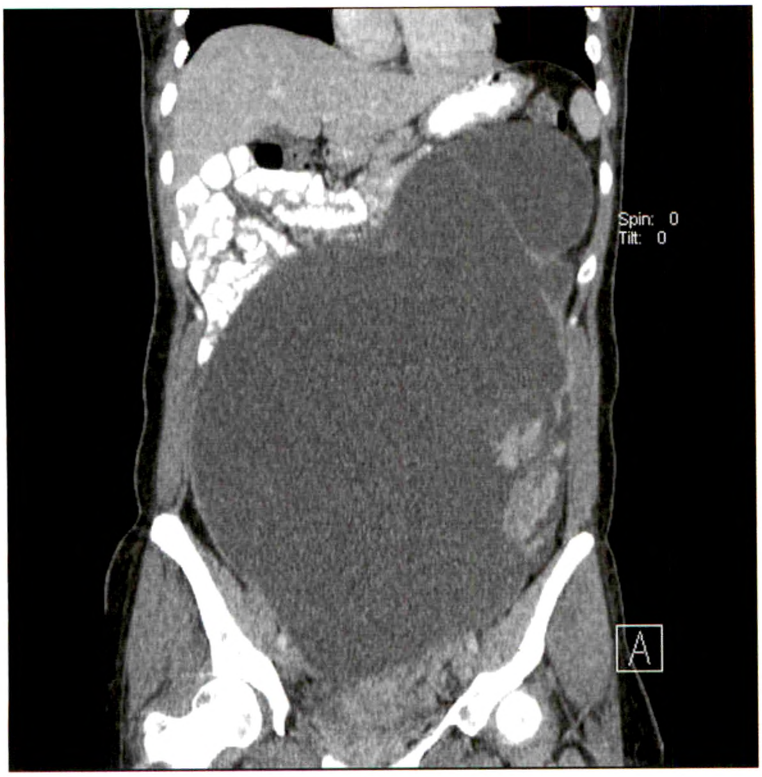

Figure 1. The abdominal CT scan. One huge cystic tumor in homogeneous internal attenuation, at least two foci of solid parts, around 4.5 cm attach to left lateral wall of the tumor.

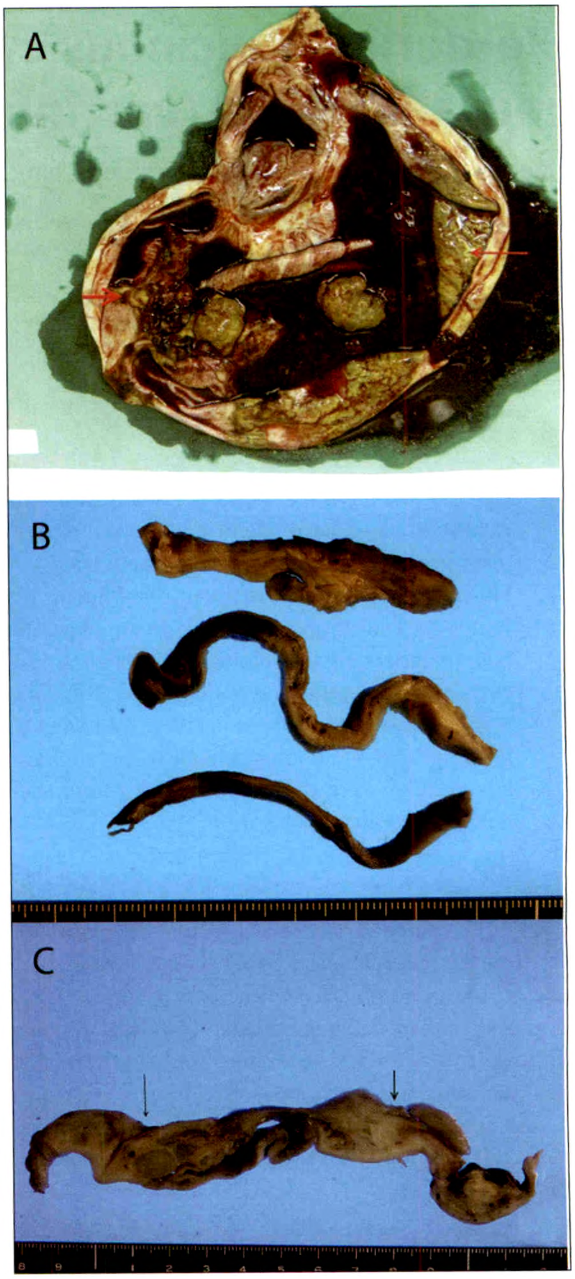

Figure 2. The cystic tumor was opened when received. Two pieces of elastic clot-like masses inside detach partially from cystic wall. A) Several yellow, solid nodules adhesive on the ovary cyst internal surface (thick arrow) and one diffuse yellow, solid patch also adhesion on internal surface (thin arrow), B) The diffuse patch measured only 0.3 cm thick. C) The septa was partially thickened with a multicystic pattern and mucous material inside (thin arrow). The mural nodule was present at the right side (thick arrow).

2A). The fallopian tube was normal on gross examination. The external surface of the cyst wall was smooth. Further examination showed two pieces of clot-like materials within the cyst wall, measuring approximately 5.5 cm in greatest dimension. The internal surface of the ovarian cyst showed multiple yellow, solid nodules measuring up to 5×4×2 cm in greatest dimension. In addition, there was also a diffuse yellow, solid area measuring approximate 25×10 cm in dimension and 0.3 cm in thickness present on the internal aspect of the cyst (**Figure 2B**). The septa were thickened up to 2.5 cm in diameter. A cross section of the septa showed multiple small cysts with a mucoid material (**Figure 2B**). Multiple sections of tumor were taken and fixed in neutral-buffered formalin and embedded in paraffin. The sections were stained with hematoxylin and eosin. Immunochemistry using cytokeratin (DAKO, AE1/AE3, 1:100) and vimentin (DAKO, 1:100) was done on some sections. Immunoreactivity was interpreted as positive or negative.

Microscopic features

The cyst was lined by mucinous epithelium showing a benign and borderline change focally with intestinal differentiation (**Figure 3A**). The multicystic cavity contained mucus materials inside. The external aspect of the cyst showed no reactive response and no evidence of rupture. The mural nodules were composed of spindle-shaped to ovoid-shaped cells with marked nuclear pleomorphism (**Figure 3B**). They had large clear nuclei with prominent nucleoli. These cells were located just below the mucinous epithelium that appeared circumscribed but devoid of a capsule. The mitotic activity was increased, and approximately 8 mitoses per 10 high-power field were recorded. Focally, there was osteoid metaplasia (**Figure 3C**). There was no evidence of vascular invasion. These spindle-shaped cells were seen to invade into the stroma of the cyst. The diffuse yellow patch seen on gross examination also contained pleomorphic spindle-shaped cells that were similar in appearance to those seen in the mural nodules (**Figure 3D**). Some large mural nodules extended toward the lumen of the cyst and showed hemorrhage, acute and chronic inflammation, and necrosis (**Figure 3E**). Immunochemistry performed showed the atypical spindle-shaped cells to exhibit strong vimentin positivity. Cytokeratin was negative. This reaction pattern was consistent with a nonepithelial component (sarcoma). Some areas were reported with several large cells that contained eosinophilic cytoplasm, and enlarged hyperchromatic and pleomorphic nuclei with large eosinophlic nucleoli. A higher magnification view of these components is shown in **Figure 3F**. Some of these cells were dispersed within the sarcoma stroma (**Figure 4A**) and some formed glandular structures (**Figure 4B**). The immunostaining performed using cytokeratin demonstrated a strong positive reaction and a negative reaction to vimentin (**Figure 4C**), confirming that they were epithelial in nature. These cells were not similar in appearance to the mucinous epithelium lining the main cyst. No transitional area was seen. The sarcoma cells were clearly distinguished from the carcinoma cells by vimentin positivity (**Figure 4D**).

The microscopic examination of the left tube showed no evidence of tumor. The abdominal washing cytology performed was negative. Based on the above findings, a borderline mucinous cystic tumor with mural nodules (carcinosarcoma), pathologic FIGO stage Ia, was diagnosed. No further biopsy or operation done after the left salpingo-oophorectomy.

After the operation, CA125 decreased to 21 U/mL in April. The patient had adjuvant chemotherapy taxotere (75 mg/m^2) and carboplatin (5AUC) every 3 weeks for 6 cycles after the operation, but had to stop because of hepatitis B exacerbation after 4 cycles of chemotherapy. After chemotherapy, CA125 decreased to 13 U/mL in December. She was followed at National Taiwan University Hospital OPD for 10 months and is free of the disease.

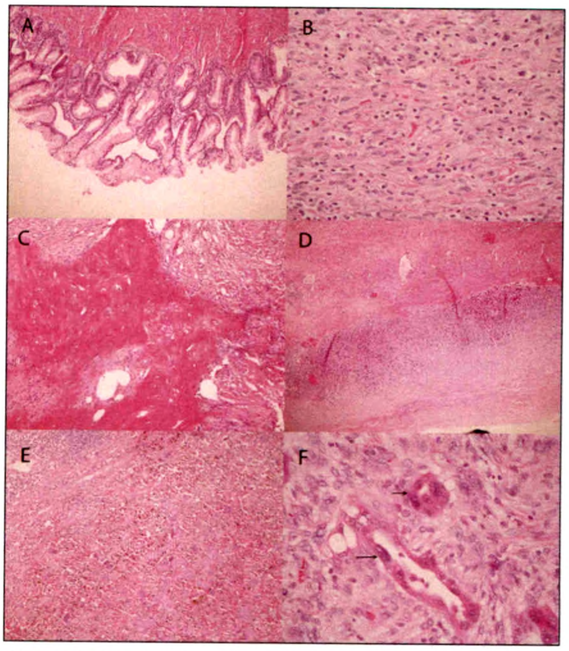

Figure 3. The epithelium cells inside mural nodules. A) Several large cells contain eosinophilic cytoplasm, enlarged hyperchromatic and pleomorphic nuclei with large eosinophlic nucleoli that are dispersed within the sarcoma stroma. B) Similar cells arranged to glandular structures (100×, HE stain). C) Immunostaining showed strong positive reaction of cytokeratin and negative reaction to vimentin. (400×). D) The stroma cells of sarcoma were clearly distinguished from the epithelium cells.

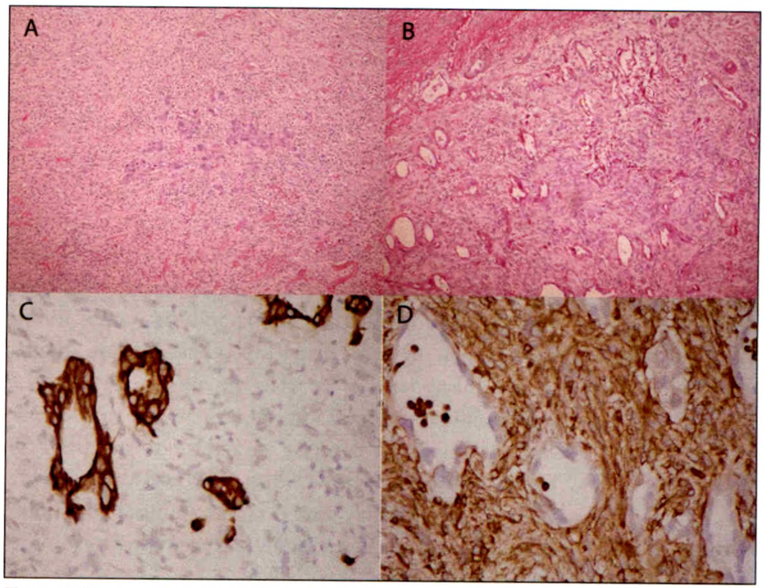

Figure 4. The components of the ovarian tumor with mural nodules. A) The cyst is lined by mucinous epithelium with focally borderline intestinal differentiation. B)The mural nodules are composed of spindle shaped cells with marked nuclear pleomorphism. C) Focal osteoid metaplasia inside mural nodules. D) The pleomorphic spindle shaped cells similar to the components inside mural nodules. E) Some large mural nodules extended toward the lumen of the cyst and showed hemorrhage, acute and chronic inflammation and necrosis (40×). F) There was a higher magnification view of the carcinosarcoma. The arrow points out the epithelial component (400×, H&E stain).

DISCUSSION

Cystic ovarian epithelial tumors with mural nodules

Table 1. The summary of previous classification and analysis of different variants of mural nodules.

Feature	Sarcoma	SLMN	Anaplastic carcinoma	Carcinosarcoma-like	Carcinosarcoma
Patient age	Older	Younger	Older	Younger	Young
FIGO stage	I-IV	Ia	I-IV	I	I-?
Prognosis	Poor	Not effective	Poor	?	?
No. of nodules	-	One to several	Usually single	One	Several
Size (cm)	Large	Small (0.6-6)	Large (1-10)	Small (1.2-5)	1.5-5.5
Circumscription	Good (grossly) Poor (micro)	Good, sharp	Poor	Poor	Variable
Vascular or stromal invasion	Present	Absent	Present	Present	Present
Cell composition	Monotonous	Heterogeneous	Homogenous	Heterogeneous	Homogenous
Inflammatory cells	Sparse	Numerous	Few, variable	Numerous	Few, variable
Giant cells	Common	Common	Uncommon	Common	Few
Spindle cells	Common	Common	Occasional	Common	Common
Large eosinophilic cells	-	Occasional	Common	Common	Common
Cytokeratin	-	Scattered, negative	Diffuse positive	Positive of carcinoma cells	Positive of carcinoma cells
Vimentin	Positive	Positive	Sometimes positive	Carcinoma: ± Stroma: +	Carcinoma: ± Stroma: +
Necrosis	Common	Often		Sometimes	

SLMN: Sarcoma-like mural nodules ?: unknown.

are rare neoplasms and were first described by Prat in 1979.[4] The epithelium of the cyst may be lined by benign, borderline, or malignant cells. Several kinds of mural nodules have been reported. They are further classified into sarcoma-like, sarcoma, and anaplastic carcinoma. Baergen et al classified mural nodules into reactive (sarcoma-like), benign, carcinoma (with a variant of combined carcinoma and reactive elements), sarcoma, and combined carcinoma and sarcoma (carcinosarcoma) in 1995.[5] The WHO Classification divided the mural nodules of ovarian mucinous cystic tumors into malignant (anaplastic carcinoma, sarcoma, or carcinosarcoma) and benign (sarcoma-like) in 2003. On review of the published studies of the serous borderline ovarian tumor with mural nodules, Gungor et al found that they were extremely rare and only five cases have been published.[1,6]

The prognosis of these cystic ovarian epithelial tumors with mural nodules is uncertain. Sarcoma-like nodules are considered to be reactive and do not affect the prognosis.[4,7] Sarcoma and anaplastic carcinoma are considered to have a poor prognosis except in cases staged as FIGO stage Ia with no tumor rupture.[5,8-10] The outcome of cystic ovarian epithelial tumors with mural nodules depends on the histology of nodules (carcinoma or sarcoma) and the stage of the disease. Thus, it is very important to determine the exact components of the mural nodules since the prognosis of these tumors is related to the histology.

As the number of these cases increased, it became easier to determine the different components within the mural nodules. The main difficulty with mural nodules arises when there is more than one component within nodules, especially sarcoma and sarcoma-like components. It is not easy to distinguish between sarcoma and sarcoma-like components within nodules since both of them contain pleomorphic cells with bizarre nuclei and many mitotic figures. The sarcoma nodules typically are seen in older patients and are large in size. They contain a monotonous cell population, showing poor circumscription, with vascular or stromal invasion and lack of inflammatory cells. On the other hand, sarcoma-like nodules show a polymorphous population of cells composed of inflammatory cells and giant cells, with no evidence of vascular or stromal invasion.[11]

Immunohistochemistry is useful to separate the

Table 2. Summary of the cases of ovarian mural nodule tumors, with new terminology and carcinosarcoma.

Reference (year)	Case	Epithelial ovarian tumor	Mural nodule	Age	FIGO stage	Therapy	Follow-up
Mural nodule tumors with new terminology, carcinoma							
Andrews et al (2008)	1	Serous, borderline	Sarcomatoid carcinoma	49	I	TAH + BSO + Omen + appen	DOD, 32 months (liver metastasis)
Chang et al (2005)	1	Mucinous borderline	Carcinosarcoma-like	35	I	TAH + BSO + Omen + appen	NED, 14 months
Bagué et al (2002)	2	Mucinous borderline	Sarcoma-like + anaplastic carcinoma	75	Ia	Surgery + ChT	NED, 15 years
		Mucinous borderline	Sarcoma-like + anaplastic carcinoma	75	Ia	Surgery + ChT	NED, 15 years
Suurmeijer (1991)	1	Mucinous carcinoma	Carcinosarcoma-like	30	I, Rupture	TAH + BSO + Omen + ChT	NED, 5 years
Søndergaard and Kaspersen (1991)	1 (Case 2)	Mucinous cystadenocarcinoma	Sarcoma-like + anaplastic carcinoma	37	I	RH + BSO + Omen + appen	NED, 18 months
Rosa et al (1991)	1	Serous, borderline	Sarcomatoid carcinoma	?	II	?	DOD, 6 months (pulmonary, bone metastasis)
McCullough et al (1988)	1	Serous, cystadenocarcinoma	Sarcomatoid carcinoma	44	III	TAH + BSO + ChT	DOD, 6 months (liver metastasis)
Fujii et al (1985)	1	Mucinous borderline	Sarcoma-like + anaplastic carcinoma	29	I	TAH + BSO	NED, 22 months
Mural nodule tumors with carcinosarcoma components							
Present case (2010)	1	Mucious borderline	Carcinosarcoma	29	Ia	USO + ChT	NED, 10 months
Søndergaard and Kaspersen (1991)	1 (Case 3)	Mucinous cystadenoma	Carcinosarcoma	29	I	RH	NED, 24 months
Bruijn et al (1987)	1	Mucinous carcinoma	Carcinosarcoma	27	Ia	USO + Omen	?

RH=radical hysterectomy; TAH=total abdominal hysterectomy; BSO=bilateral salpingo-oophorectomy; USO=unilateral salpingo-oophorectomy; appen=appendectomy; Omen=omentectomy; ChT=chemotherapy; DOD=died of disease; NED=no evidence of disease; ?=unknown

components within the mural nodules. Before the advent of immunohistochemistry, some carcinoma nodules were misdiagnosed as sarcoma-like (reactive). When using cytokeratin, the positive epithelial cells are identified within the bizarre stromal components of the nodules. On the other hand, immunohistochemistry is not useful to distinguish sarcoma and sarcoma-like nodules since vimentin is positive and cytokeratin is negative in both malignant and reactive components of the nodules.

The age of the patient, prognosis, histologic features, and immunohistochemistry reaction for various mural nodules are summarized in **Table 1**.[5,8,9] The summary here is useful for making the differential diagnosis of the components within the nodules, but exceptions do occur. Within the last 30 years, the terminology used to describe carcinoma and carcinosarcoma components of mural nodules has been somewhat confusing. We reviewed the published studies, and in particular looked at the histology and immunohistochemistry of tumors with mural nodules where the diagnoses of sarcomatoid carcinoma[6,12,13] and carcinosarcoma-like[14,15] were made. After analysis of the histology and immunohistochemistry, sarcomatoid carcinoma and carcinosarcoma-like tumors were found to be epithelial in nature and represent carcinoma. The cases of sarcomatoid carcinoma have epithelial cells that are often spindle shaped. These epithelial spindle cells and the transition zone between glandular epithelial cells and the stroma cells are cytokeratin positive. The transition zone was not present in our case. Two cases were described in 1991 and 2005[14,15] using the term carcinosarcoma-like, and they described features of carcinoma and sarcoma-like (reactive) elements. In our case, there were malignant stroma cells (sarcoma). Only two real carcinosarcoma cases have been previously published.[2,3] The mural nodule tumors used new terminology that we reclassified as carcinoma and carcinosarcoma. They are summarized in **Table 2.**[2,3,6,12-17]

Mucinous cystic ovarian tumor with mural nodules should be distinguished from malignant mixed mesodermal tumor (MMMT). MMMT is usually a solid neoplasm composed of epithelial and stromal elements. These elements usually do not merge with each other. It is also unusual to find mucinous epithelium in an MMMT. Moreover, MMMT occurs almost exclusively in older patients. In our case, there were several mural nodules. The cyst was lined by mucinous epithelium with subepithelial sarcoma. Some mural nodules had a patch-like appearance. The sarcoma invaded the stroma of the cyst. The sarcoma stroma contained pleomorphic spindle cells with no inflammatory cells. Foci of osteoid metaplasia were present. No evidence of vascular invasion was reported. The eosinophilic large cells dispersed within sarcoma stroma were cytokeratin positive, confirming their epithelial nature (carcinoma).

Reports of carcinosarcoma elements inside mural nodules are rare. A review of the published studies reveals that the mural nodules with anaplastic carcinoma usually had a poor prognosis and were seen in older patients. The two cases shown in **Table 2** reveal that carcinosarcoma occurred in young patients (27 and 29 years old). One was alive well after 24 months of follow-up and the other one was lost to follow-up. Thus, follow-up was only available for two patients including our case. The follow-up periods were also not long enough (24 and 10 months) to ascertain prognosis.

Mural nodules are rarely identified in ovarian cystic tumors, and thus the prognosis is not well defined. It is surprising that even the carcinosarcoma cases also had anaplastic carcinoma components inside. They occur in patients of younger age (below 30 years), and the patients have a relatively better clinical outcome. Because of the above reasons, the existence of sarcoma combined with carcinoma components in mural nodules necessitates careful examination, as the outcome of the tumor depends on the histology.

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Anti-NMDA-receptor encephalitis presenting as postpartum psychosis in a young woman, treated with rituximab

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A severe paraneoplastic form of acute encephalitis associated with antibodies against the N-methyl D-aspartate (NMDA) receptor typically occurs in young individuals and is associated, but not always, with an underlying tumor. If diagnosed early, initiation of immunotherapy and tumor removal (if present) may result in recovery. We report a case in a 25-year-old young woman who presented to our medical center with postpartum psychosis. Treatment with rituximab (a chimeric monoclonal antibody against the protein CD20) resulted in gradual improvement in mental status and resolution of seizure activity episodes. A year after diagnosis and treatment, the patient was doing well without recurrences, and no tumors appeared. This is the first described case of anti–NMDA-receptor antibodies encephalitis that presented initially as a postpartum psychosis disorder and was successfully treated with rituximab.

N-methyl D-aspartate (NMDA) receptors are ligand-gated cation channels whose function centers around synaptic transmission and plasticity.[1] The receptors are heteromers of NR1 subunits that bind glycine and NR2 (A, B, C, or D) subunits that bind glutamate. NR1 and NR2 combine to form receptor subtypes, and their pharmacological properties include localization and the ability to interact with intracellular messengers; they also have the ability to interact with intracellular messengers.[2] Hyperactivity of these NMDA receptors results in neuropsychiatric excitotoxicity, which can manifest clinically as epilepsy, dementia, and stroke; whereas hypoactivity produces symptoms of schizophrenia.[3] Anti-N-methyl-D-aspartate (anti-NMDA)-receptor encephalitis is a recently described neurological condition with antibodies against NR1-NR2 heteromers. It is composed of a well-defined set of clinical features that have been characterized in adults, frequently in young women, with teratomas of the ovary who develop changes of mood, behavior, and personality, resembling acute psychosis.[4] The clinical picture usually progresses to include seizures, a decreased level of consciousness, dyskinesias, autonomic instability, and hypoventilation.[5] Removal of the teratoma, immunotherapy, plasma exchange, intravenous immunoglobulin (IVIG), and corticosteroids have resulted in clinical improvement regardless of the severity of the encephalitis. This is suggestive of an underlying autoimmune component to the pathogenesis.[6] We report a case of anti-NMDA-receptor encephalitis in a woman whose initial clinical presentation was that of acute postpartum psychosis.

CASE

A 25-year-old female with no significant medical history presented with bizarre behavior and recurrent seizures. She stated that 1 week prior to admission, she had a flu-like illness associated with rhinorrhea and generalized malaise. She had given birth by normal vaginal delivery to a healthy boy 2 months ago. She subsequently developed status epilepticus with generalized tonic-clonic activity, which was treated with lorazepam 4 mg and phenytoin 1000 mg intravenously. She developed hypoventilation and had to be intubated. Her vital signs were stable, and physical examination, routine hematologic, studies and urine toxicology screening provided normal results. The head computed tomography (CT) scan was unremarkable; the cerebrospinal fluid (CSF) analysis showed white blood cell count of 111 cells/mL (normal 0-3 cells/mL) [lymphocytes 95%], red blood cell 1 cell/mL (normal o); protein 61 mg/dL (normal 15-45 mg/dL); glucose 64 mg/dL (normal 50-80 mg/dl). Serum glucose was 111 mg/dL. The erythrocyte sedimentation rate was 75 millimeters/hour (normal 3-5 mm/hr); antinuclear antibody, negative; rapid human immunodeficiency virus enzyme-linked immunosorbent assay, negative; rapid plasma reagin and the Venereal Disease Research Laboratory test, were negative. Tests for Lyme disease, Epstein-Barr virus, and arboviruses were negative. An autoimmunity panel of tests (including, among others, anti-double-stranded DNA, thyroid peroxidase, and anti-neutrophil cytoplasmic antibodies) were negative. CT scans of the chest, abdomen, and pelvis; and a PET scan were all unremarkable. She also had an endoscopy with jejunal biopsy, which was negative for Tropheryma whippelii. Acyclovir 10 mg/kg body weight every 8 hours was started empirically for herpes simplex virus (HSV) encephalitis. The magnetic resonance imaging (MRI) of the brain was negative. An electroencephalogram (EEG) showed severe diffuse slowing consistent with a diffuse encephalopathic state with an absence of epileptiform activity. The patient was started on methylprednisolone 1 g IV daily. On the CSF analysis, the HSV polymerase chain reaction (PCR) was negative, and acyclovir was discontinued. Cytomegalovirus and West Nile PCR were also negative. The CSF anti-Ma and anti-voltage-gated potassium-channel antibodies were negative; however, the anti-NMDA-receptor antibodies were positive. The patient was started on plasmapharesis. One week later, there was no improvement; therefore, rituximab was added to the regimen. The patient's mental status gradually improved, and she became more alert and was weaned off the ventilator. She was discharged home on levetiracetam 500 mg twice daily; and 2 months later, her cognitive functions, memory, and results of neuropsychiatric evaluation were completely normal.

DISCUSSIONS

Anti-NMDA-receptor antibodies bind to the NR2B or NR2A subunits of NMDA receptor. NR2B binds glutamate and is avidly expressed in the hippocampal and forebrain neurons of humans. These antibodies inhibit NMDA receptors in presynaptic gamma-aminobutyric acid (GABA)ergic interneurons, resulting in reduced GABA release and disinhibition of postsynaptic glutamatergic transmission with excessive release of glutamate in the prefrontal/subcortical structures. The pathogenic role of these antibodies is further strengthened by their disappearance during clinical improvement.[7] Anti–NMDA-receptor encephalitis is a treatable paraneoplastic neurologic condition that predominantly affects young women. It is characterized by a constellation of symptoms, which include psychotic encephalopathy, seizures, and abnormal movements of the trunk and face, particularly in the form of jaw dystonia.[8] With progression of the disease, patients frequently become catatonic and unresponsive to verbal commands, and then they commonly begin to display hyperkinesias and lingual-facial-buccal dyskinesias, as well as hypoventilation.[9] Early recognition of the typical clinical presentation can increase the index of suspicion and facilitate early and prompt initiation of appropriate therapy. Prüss et al recommended that all young patients admitted to the intensive care unit with encephalitic signs (like psychiatric symptoms and seizures) be tested for anti-NMDA-receptor antibodies.[10] The analysis of CSF typically reveals pleocytosis, increased protein concentration, and a high IgG index.[11] EEGs occasionally show epileptiform abnormalities, but usually reveal only diffuse slowing of the brain waves.[12] Most cases (75%) have either normal or atypical brain MRI findings with mild abnormalities surrounding the medial temporal lobes, often with cortical enhancement. The brain MRI may show transient fluid-attenuated inversion recovery or contrast-enhancing abnormalities in the cortical (brain, cerebellum) or subcortical (hippocampus, basal ganglia, white matter) regions. Hybrid F-18 fluorodeoxyglucose positron emission tomography (PET) is particularly useful to screen for an associated tumor in the absence of brain MRI findings. Though encephalitis associated with NMDA-receptor antibodies is potentially fatal, there is typically rapid symptomatic relief with immunosuppressive therapy, and it resolves entirely with tumor removal.[13]

The ideal management of anti-NMDA-receptor encephalitis is tumor resection and immunotherapy. Patients with this disorder, however, usually require ventilatory support and intensive care for seizures and autonomic instability, which can delay tumor removal.[14] Treatment with methylprednisolone, plasma exchange, or IVIG might result in partial or complete amelioration of neurologic symptoms or in stabilization allowing resection, although the tumor could grow during the delay.[15] In some patients, tumor removal results in noticeable neurological improvement in a matter of days or after several weeks. Our patient, after diagnosis, was treated with plasma exchange, steroids, and IVIG with minimal improvement. Dramatic improvement was noted after initiation of rituximab. Patients (often, those without a tumor) who do not improve with typical first-line therapies may improve with rituximab and/or cyclophosphamide.[16]

Progressive neurologic deterioration and death can occur without treatment. However, spontaneous recovery has also been described in a few patients after several months of severe symptoms. Relapse occurs in 15% to 20% of the patients and is often associated with occult or relapsing teratoma or with the absence of a tumor.[17]

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Takotsubo cardiomyopathy resembling acute high lateral myocardial infarction

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A 65-year-old female patient admitted to the emergency department was diagnosed with acute high lateral myocardial infarction, but later Takotsubo cardiomyopathy (TC) was discovered. She had squeezing chest pain that started shortly after an emotional stress. The electrocardiogram revealed a loss of R wave voltage in leads V1 to V4 and an ST-segment elevation in I and aVL. After an urgent coronary angiography and ventriculography, TC was considered, and supportive anti-ischemic treatment was started. The severe left ventricular systolic dysfunction improved and normalized during the follow-up. She was discharged without any complications. TC is a new entity of acute cardiac events, and patients usually recover completely without sequelae with proper diagnosis and management. An exact diagnosis may also prevent an inappropriate application in the setting of recurrences.

Takotsubo cardiomyopathy (TC), also known as transient left ventricular apical ballooning syndrome, is one of the acute cardiac events that resemble acute coronary syndromes. The characteristics of this syndrome are electrocardiographic ST-T changes mimicking acute coronary syndromes, reversible wall motion abnormalities that cannot be explained by a single major coronary artery occlusion, and increased cardiac enzymes, but absence of obstructive or thrombotic lesions on coronary angiography. We present a TC case mimicking acute high lateral myocardial infarction (MI).

CASE

A 65-year-old female patient without any medical history was admitted to our emergency department with a complaint of mild squeezing chest pain lasting 1 hour. Her chest pain started soon after an emotional stress, when she learned that her mother had died. The heart rate and blood pressure were 79 bpm and 130/80 mm Hg, respectively. The physical examination was normal. The electrocardiogram (ECG) revealed a loss of R wave voltage in leads V1 to V4 and a 0.5 mV ST-segment elevation in I and aVL, without any reciprocal changes (**Figure 1a**). The corrected QT (QTc) interval was 464 ms. An urgent coronary angiography showed only a nonobstructive proximal left anterior descending coronary artery plaque without any coronary spasm, but the left ventriculography revealed characteristic apical ballooning due to hyperkinesis of basal segments and akinesis of other segments (**Figure 2**). The left ventricular end diastolic pressure was 10 mm Hg.

At bedside, the transthoracic echocardiography (TTE) in the intensive care unit showed a severely depressed left ventricular systolic function with an ejection fraction (EF) of approximately 20% to 25%. The mid and apical segments of all left ventricular walls were akinetic, while basal segments were hyperkinetic (**Figure 3**). The peak troponin I level was found as 4.97 ng/dL (reference 0-0.06 ng/dL) during hospitalization. Fasting glucose, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, and triglyceride levels were 98 mg/dL, 102 mg/dL, 50 mg/dL, 18 mg/dL, and 90 mg/dL, respectively. She had no history of cigarette smoking or any drug usage. The left ventricular systolic functions showed progression during serial TTE examinations under acetylsalicylic acid, clopidogrel, and metoprolol treatment without any inotropic support. She was discharged from the hospital with dual antiplatelet and beta-blocker medications at the end of the first week, with a possible diagnosis of TC. During serial visits, the TTE showed a progressive improvement and normalization of wall motion 2 weeks after the index event (**Figure 3**). The EF was calculated as 60%-65%. The ECG at that time showed a normal R wave progression in precordial leads, inverted T waves in leads I, aVL, and V1to V6, and a positive T wave in aVR (**Figure 1b**). The QTc was calculated as 436 ms at that time.Thus, she was diagnosed with TC. The patient did not experience health problems over a 3-month follow-up period.

DISCUSSION

TC was first described in the Japanese population in 1990, and it is seen far more commonly in Japan.[1] However, folllowing increased awareness of the syndrome more patients with TC were reported in Europe and North America. The mean age was reported as 67 years in one of the largest series.[2] According to that study, 63% of the patients had physiologic or emotional stress and 86% of cases were women. Chest pain was the most common presenting symptom (67%), but isolated dyspnea or syncope was also reported in the published studies.[3] The ST-segment elevation is seen frequently on admission (90%), especially in precordial leads, yet the isolated ST elevation in inferior or lateral leads is seen rarely.[2] In the same study, which had a relatively large patient number, Tsuchihashi et al found that creatinine kinase was elevated in 56% of cases,[2] but some of later series using troponin as a cardiac marker showed elevation of that cardiac biomarker in virtually all patients.[4] The peak level of troponin in TC patients is generally disproportionately low given the extent of wall motion abnormality, and almost all patients typically develop T-wave inversions in most leads on the subsequent days.[2]

The transient wall motion abnormality (akinesis or dyskinesis) usually affects apical and mid portions of the left ventricle. However, some variant TC cases in the published studies propose that the apical wall motion may be spared in some patients.[5,6] It was shown that no ECG criteria can reliably discriminate between TC and ST-segment elevation MI.[7] Although no single noninvasive techniques are available for differentiation of these two entities, cardiac MRI may be helpful. Some studies showed that in contrast to the typical findings in acute MI or myocarditis, TC patients do not show any delayed gadolinium hyperenhancement.[8,9] Still, an invasive coronary arteriography is usually needed in most patients in routine clinical practice.

The precise etiology and real frequency of the syndrome are not known. Since the syndrome commonly occurs immediately after an acute emotional and/or physical stress, catecholamine stimulation seems to be an important component of the pathophysiology of TC. Wittstein et al showed that patients with TC have 2- to 3-fold higher catecholamine levels compared to acute MI patients who have the same degree of heart failure.[10] Furthermore, the endomyocardial biopsy of TC patients showed mononuclear infiltrates and contraction-band necrosis, which are consistent with the catecholamine-mediated cardiotoxicity.[10]

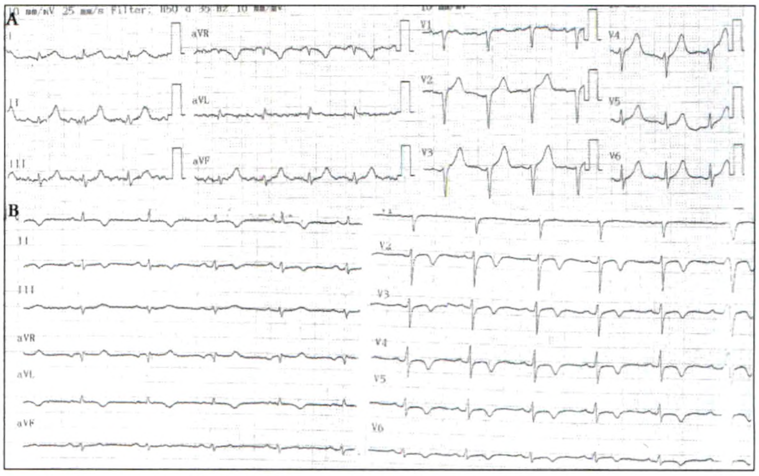

Figure 1. Twelve lead electrocardiogram (ECG) showing minimal 0.5 mm ST segment elevation in leads aVL, I and loss of R wave voltage in leads V1-V4 (A). Twelve lead ECG showing restoration of R wave voltages in precordial leads and typical negative T waves in most of the leads (B).

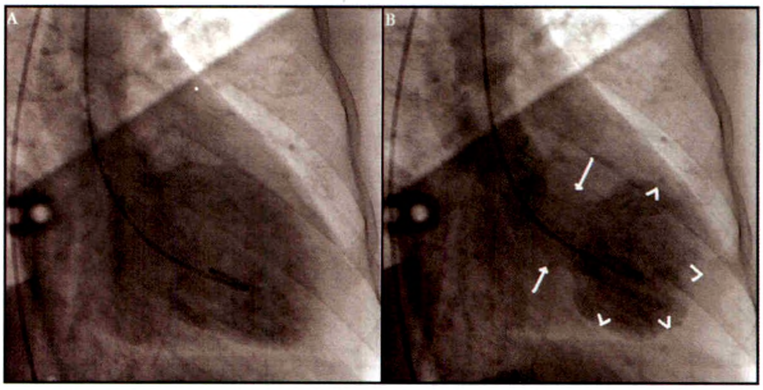

Figure 2. Left ventriculogram in the right anterior oblique projection during diastole (A) and systole (B) showing akinesis of the midventricular and apical segments (arrowheads) but hyperkinesis of basal segments (arrows) giving the shape of apical ballooning.

Overall, the prognosis seems favorable. In the largest series including 88 patients, the mortality rate was reported to be 1%.[2] In the same study, heart failure or pulmonary edema were seen in 22% of patients, and 8% of cases needed intra-aortic balloon pump. Eight patients (9%) exhibited ventricular tachycardia or fibrillation. Only 1 patient (1%) had heart failure at discharge, and recurrences of TC were seen in 2 patients (2%) after discharge. However, some rare complications, such as left ventricular wall rupture and severe mitral regurgitation due to acute rupture of the posteromedial papillary muscle, were also reported in published studies.[11,12]

After prediagnosis, classical heart failure treatment including diuretics, inotropics, angiotensin-converting enzyme inhibitors, beta-blockers, and antiplatelet agents should be started and, if needed, left ventricular assist devices should be used.[13] While considering the inotropic support, clinicians should also be aware of the dynamic intraventricular obstruction due to hyperkinesis of basal segments, systolic anterior motion of mitral leaflets and chorda (SAM). This complication is seen in 18% of patients and may worsen after positive inotropic support by increasing the gradient or a worsening of possible mitral regurgitation caused by SAM.[2] The ventricular mural thrombus formation and thromboemboli are potential complications especially in those with the significant left ventricular systolic dysfunction.[14] Thus, short-term anticoagulation should be considered in most patients until the recovery of wall motions begins.[4]

In conclusion, TC is a recently defined acute cardiac event and should be suspected especially in individuals without an obvious heart disease. Despite its dramatic presentation, usually patients recover completely without sequelae with proper diagnosis and management. Since some recurrent TC cases were defined,[15] an exact diagnosis during the index event will also prevent inappropriate applications in the setting of recurrences.

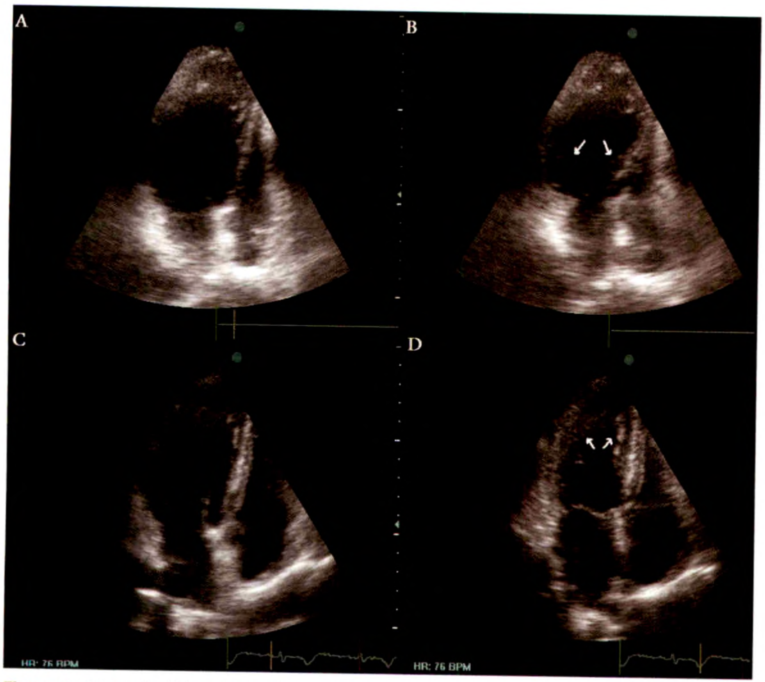

Figure 3. Diastolic (A) and systolic (B) frames of apical 4-chamber view of transthorasic echocardiography in intensive care unit showing akinetic mid and apical segments and hyperkinetic basal segments (arrows). After serial visits, apical 4-chamber view of control transthoracic echocardiography showing normal left ventricular wall motions during diastole (C) and systole (D). Arrows indicate normal thickening of previously abnormal segments

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case report

Revisiting fetus-in-fetu

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Fetus-in-fetu is a rare congenital anomaly in which a malformed parasitic twin is found within the body of its partner. Less than 100 cases have been reported in published studies. Although it is a relatively benign condition, clinicians need to have a high index of suspicion for the associated complications that may arise. We report the case of an infant presenting with jaundice and steadily growing abdominal mass, who was diagnosed with fetus-in-fetu syndrome. We review the published studies and discuss the pathophysiology, complexities, and management options.

Fetus-in-fetu is an extremely uncommon cause of abdominal mass in the neonate, presenting as an encapsulated and pedunculated vertebrate fetoid mass in the abdomen usually from birth.[1] Less than 100 cases have been reported in the published studies. There is a male preponderance (male: female 2:1),[2] and about two-thirds of the cases present before 2 years of age. The presence of such an entity may lead to various manifestations secondary to mass effect on the adjacent viscera (obstructive jaundice in our case). We report a case of an infant presenting with mass abdomen and jaundice, and on evaluation was found to be fetus-in-fetu. We review the published studies and attempt to throw light on the possible pathophysiologic mechanisms, the manifestations, and management.

CASE

We report a case, in retrospect (1974), of an 11-month-old infant who presented with mass abdomen, failure to thrive, recurrent vomiting, and jaundice from about 4 months of age. He was a product of a non-consanguineous marriage and was born full term by normal spontaneous vaginal delivery. The abdominal mass had been steadily increasing in size with progressive worsening of the associated symptoms. The weight of the baby was 7.8 kg. The examination revealed icterus and mild pallor. Vital signs were unremarkable. The abdominal exam revealed an irregular mass on palpation, spanning from the left hypochondrium to the iliac fossa, and multiple irregular, firm to bony masses palpable all over the abdomen. A plain abdominal x-ray taken in 1974 showed multiple calcific/ossific densities on either side of the abdomen with evidence of long bones of limbs (**Figure 1**). (Further investigations like computed tomography (CT) and ultrasonography (USG) were not available at that time). The intravenous pyelogram depicted good excretion on both sides, showing a normal collecting system on the left side with evidence of hydronephrosis

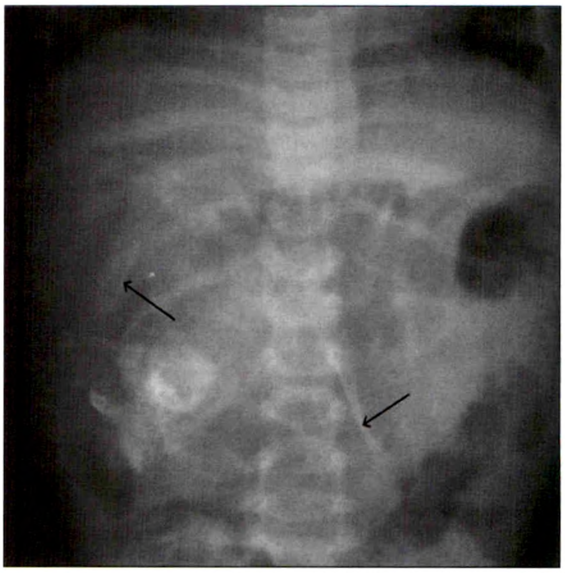

Figure 1. Plain abdominal x-ray showing multiple calcific/ossific densities on either side of the abdomen with evidence of long bones of limbs.

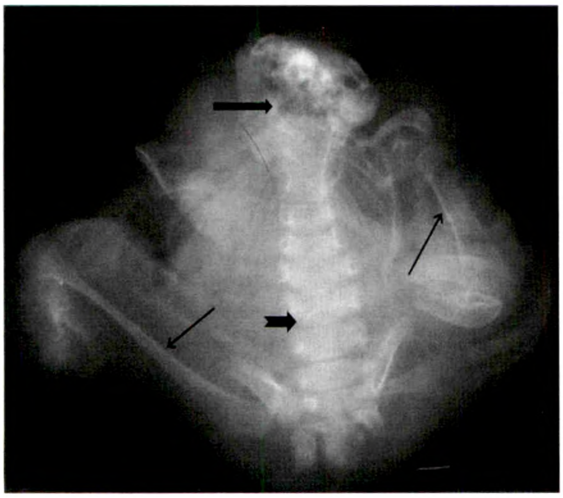

Figure 2. Radiograph of the specimen (post operative) delineating the fetus's spine (broken arrow), upper and lower limbs (thin arrows) with evidence of anencephaly (thick arrow).

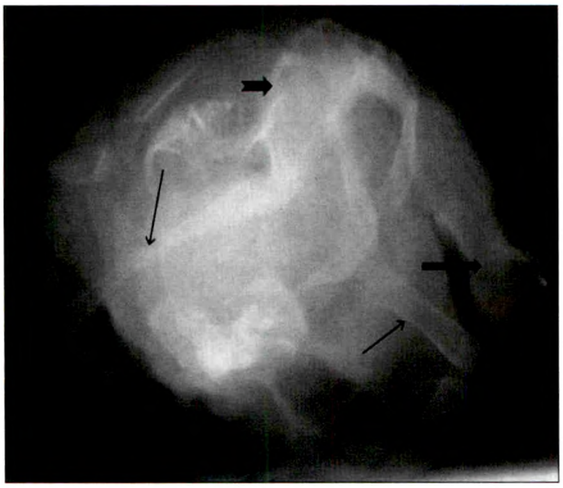

Figure 3. Post-operative radiograph of the specimen confirming Fetus-in-fetu disorder with evidence of spine (broken arrow), upper and lower limbs (thin arrows) and anencephaly (thick arrow).

and upward and lateral displacement of the right kidney by the calcific/ossific density mass. The patient's liver function tests were deranged (total bilirubin 5.3 mg/dL [normal 0.3 to 1.9 mg/dL], direct bilirubin 3.8 mg/dL [normal 0 to 0.3 mg/dL], alkaline phosphatase 385 U/L [normal 45-125 U/L]). Other lab tests were essentially normal. The surgical evacuation of the mass grossly showed features of a fetus having upper and lower limbs with anencephaly. Radiographs of the specimen further delineated the fetus's spine (broken arrow in **Figures 2 and 3**), upper and lower limbs (thin arrows in Figures 2 and 3), and evidence of anencephaly (thick arrow in Figures 2 and 3). On follow-up after 2 weeks, the patient's jaundice significantly improved and he was doing well.

DISCUSSION

Fetus-in-fetu is hypothesized to result from an unequal division of the totipotential inner cell mass of the developing blastocyst, leading to the inclusion of a smaller cell mass within a maturing sister embryo.[3] The aborted or suppressed monozygotic twin (monoamniotic, monochorionic) later develops vitelline circulation anastomoses[4] ultimately resulting in partial or complete external morphologic characteristics of a human form. Although a single fetus-in-fetu is the usual presentation, there have been reports of 2,[5] 3,[6] 5[7] or more fetuses in the published studies. The vascular dominance of the host twin or, at times, an inherent defect in the parasitic twin will hamper the growth of the fetus-in-fetu which, initially in utero, parallels that of the host twin. Although an accurate preoperative diagnosis is not difficult most of the time, in some cases only a laparotomy can clinch the diagnosis. The diagnosis in our case was especially difficult, given the paucity of investigations at that time (1974). It is mostly found in the retroperitoneum, but has also been reported to occur in the cranial cavity,[8] lateral ventricles, scrotum,[8] testicles,[9] pelvis,[6] iliac mesentery,[10] adrenal, coccyx,[11] and inguinal region.[12] The symptoms (from the mass effect) usually are abdominal distention, difficulty in feeding, vomiting, jaundice, and urinary retention. Differentiating from the much more frequent, highly organized, and well-differentiated teratoma, which is a true tumor with a distinct malignant potential, is of paramount importance as the prognostic implications vary drastically. Grossly, the amniotic-like sac appearance, fine hair-bearing skin covering the whole specimen, and vestigial limbs or organs appropriately arranged with respect to the vertebral axis help in distinguishing it from a teratoma. Most authors opine that the presence of a vertebral column/neural tube, an amnion or umbilical cord, tissue indigenous to an embryo/fetus, and a high degree of structural organization (organoaxial orientation) differentiates the entity from teratomas. There are reports of "pseudofetu" or a sacrococcygeal teratoma without a verebral column, but with rudimentary organs and other such presentations that argue the possibility of an overlap or entities representing the same pathology at different stages of maturation (about 9% of the cases do not have a well-defined vertebral axis). There have been case reports of a fetus-in-fetu and a teratoma occurring in the same patient reinforcing such theories. Both these entities may present with different degrees of spinal dysgenesis or residual posterior enteric remnants secondary to early focal disturbance of endodermal-ectodermal differentiation.[13] The other differentials include Wilm tumor, neuroblastoma, and hydronephrotic kidney.

Almost every organ in fetus-in fetu is deformed due to hypoxia, with anencephaly being common. Although the body is closed most of the time, ventral defects, like omphalocele, are not uncommon.[7] Usually, the host does not manifest with any anomalies other than those related to the presence of a space-occupying lesion. Malignant degeneration has never been reported and appears highly unlikely. Saponification and skeletonization of fetuses, as occurs in a longstanding abdominal pregnancy, have not been described in cases of fetus-in-fetu for mechanisms that are unclear.[14] USG commonly shows a well-delineated capsule, with an echogenic mass suspended/partially surrounded in fluid and occasionally a rudimentary spine.[15] CT and other imaging modalities may better delineate the long bones, spine, and appendages of the mass.

Treatment includes excision of the fetus with its capsule, and usually the mass is easily removed from the loosely adherent adjacent structures. The complete excision curbs the problems associated with increasing size, local pressure, hemorrhage into cystic mass, and uncertainty about diagnosis. The outcome is generally excellent. The child needs to be adequately followed up. Fetus-in-fetu is a very rare entity, but warrants a place in the differential diagnoses of abdominal mass in a child. Although mostly benign, the possible co-occurrence of a teratoma mandates surgical removal of the mass and the prognosis is mostly good.

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case report

Lethal *Legionella* infection in an immunocompromised child: first reported case in the Middle East

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Legionnaires disease continues to be underreported in the Middle East — a reflection of underdiagnosis, both clinically and by laboratory investigations. We draw the attention to this unusual cause of occasionally fatal, yet severe, pneumonia by reporting an immunocompromised infant who succumbed to *Legionella pneumophila* pneumonia. The urinary test for *Legionella* antigen was positive, and this was then confirmed by a bronchoalveolar fluid culture. Moreover we have reviewed the incidence, pathophysiology, association with immunodeficiency, diagnostic tools, and treatment in this case report.

Pulmonary infections are common among patients with altered host immunity. In addition to the common bacterial, fungal, and viral infections, *Legionella* is a well-recognized causative agent. An outbreak of an unusual organism in 1976 resulted in the death of 29 participants (16%) of the annual convention of the American Legion in Philadelphia.[1] About 6 months later, a new fastidious gram-negative bacillus was isolated from the pulmonary tissue of some of those who died. In recognition of the historical association with the American Legion Convention, this disease was named legionnaires disease (LD).

In retrospect, several prior unsolved outbreaks of pneumonia were soon learned to be LD, including outbreaks in the 1950s and 1960s. In addition, an unidentified organism isolated from a patient's blood in 1947 was shown to be *Legionella* bozemanii many years later.[2] Since then, the *Legionella* is a well-established etiologic agent of both community and hospital-acquired pneumonias. Currently, more than fifty species of the family Legionellaceae have been identified. *Legionella* pneumophila alone causes approximately 90% of human infections. *Legionella micdadei* and *Legionella dunoffi* are the second and third most common species to cause LD in children, respectively.[3] Risk factors for LD in children following exposure include immunocompromised status, especially, corticosteroid treatment and chronic pulmonary disease. In this report, we describe a case of a 13-month-old girl who was on adrenocorticotropic hormone (ACTH) treatment for infantile spasms. She developed severe *L pneumophila* pneumonia that lead to respiratory failure, severe acute respiratory distress syndrome (ARDS), and death.

CASE

A 13-month-old girl was admitted to our hospital with a high-grade fever and difficulty in breathing for a few hours previously. The chest radiograph (**Figure 1**) showed the presence of air-space disease affecting the upper zone of the right lung. The past medical history revealed a diagnosis of infantile spasm at the age of 11 months, and she had been on the ACTH therapy for the previous 6 weeks. The adverse effect of the ACTH therapy was apparent with a cushingoid appearance and high cortisol levels in the blood (7460 mmol/L). The patient was admitted to the pediatric ward with the impression of aspiration pneumonia and was started on empirical antibiotic treatment (intravenous ceftriaxone and clindamycin). Initially, the patient was normoxemic on room air; however, after 2 days of hospitalization, respiratory distress progressed with an increase in oxygen requirement. As a result of clinical deterioration, antimicrobial treatment was intensified that included intravenous vancomycin, meropenem, fluconazole, and erythromycin.

As the patient continued to deteriorate, she was transferred to the pediatric intensive care unit, where a hypoxemic respiratory failure resulted in intubation and mechanical ventilation. A bronchoalveolar lavage (BAL) effluent was clear in color, and special stains for acid-fast bacilli, fungi, and *Pneumocystis carinii* were negative, with no evidence of viral cytopathy. BAL fluid multiplex polymerase chain reaction (PCR) detected *L pneumophila*. This was confirmed by *Legionella* culture specimens. A *Legionella* urine antigen enzyme immunoassay (EIA) test was also positive. Accordingly, her antibiotics were changed to azithromycin, rifampicin, and ciprafloxacillin. The patient progressed to ARDS, and she had failure of ventilation on conventional mechanical ventilator. A high frequency oscillatory ventilation (HFOV) was initiated and nitric oxide was added. She also developed a severe hemodynamic instability that required escalating doses of dopamine and epinephrine. The patient continued to deteriorate in the form of hypoxemia and severe respiratory failure not responding to high settings of HFOV, prone positioning, and nitric oxide. Her ARDS continued to worsen (**Figure 2**) and eventually led to her death.

DISCUSSION

In adults, LD accounts for 2% to 9% of community-acquired pneumonias.[4] The true incidence of this disease in children is unknown, as most of the infections have been reported as scattered case reports.

The environmental reservoir of *Legionella* in nature is fresh water. The growth of *Legionella* occurs more readily in warm water. Air conditioned and cooling towers continue to be the most frequently suspected sources in reported community-acquired outbreaks. Modes of transmission of *Legionella* to humans include inhalation of aerosols containing *Legionella*,[5] and aspiration of water contaminated with the organism.[6]

The primary host defense mechanism against *Legionella* is the cell-mediated immunity. Similar to other intracellular pathogens, depression of cell-mediated immunity by glucocorticoids and immunosuppressive drugs poses a high risk for infection[7] by interfering with T cells and macrophage functions. Glucocorticoids have known suppressive effects on the immune system. They alter the population of circulating leukocytes and decrease the number of lymphocytes and monocytes.[8] In addition to affecting cell numbers, steroids also reduce cellular functions. Glucocorticoids inhibit the system of multiple cytokines including interferon gamma and interleukin-2 that may lead to subsequent inhibition of activation and proliferation of T lymphocytes. Thus, the use of glucocorticoids has long been suspected to predispose patients to unusual infections.

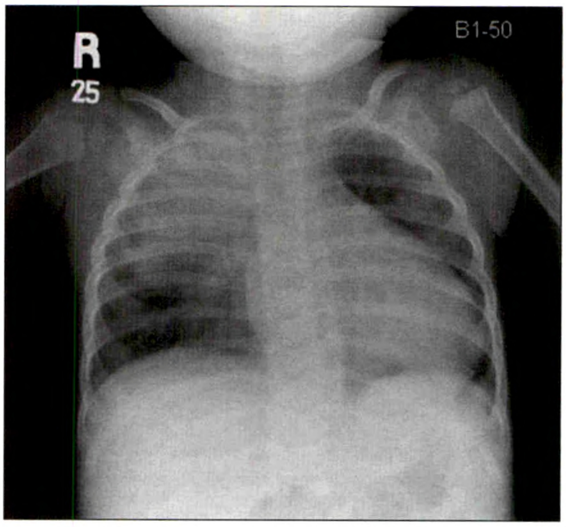

Figure 1. Chest x-ray upon admission to hospital.

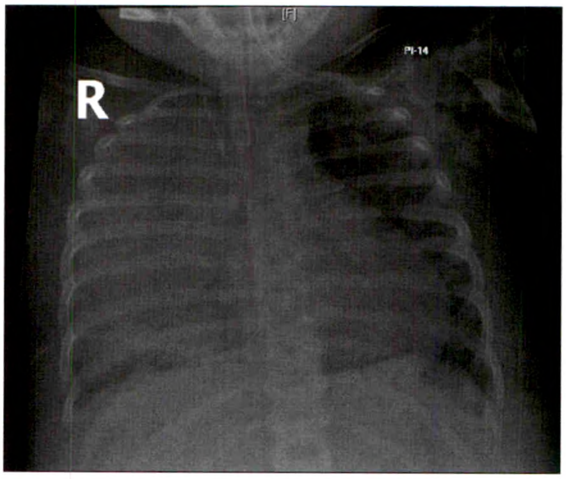

Figure 2. Chest x-ray on day of death.

Many case reports in the published studies addressed the link between glucocorticoid therapy and *Legionella* pneumonia. Garcia et al,[9] in 2004, reported a fatal case of *Legionella* pneumonia in a case of systemic lupus erythematosus treated with steroids. Abernathy-Carver et al described two cases of *Legionella* pneumonia (*L pneumohilia and L micdadei*) occurring in children with bronchial asthma receiving high-dose systemic steroids.[10] The only similar case to that of ours was described by Le Francois et al, in 1989, when they reported a case of infantile spasms in an infant aged 8 months who was treated with ACTH for 4 weeks and then died because of severe *L pneumohilia* pneumonia.[11]

Isolation of *Legionella* species by culture is considered the gold standard for the diagnosis of LD with a specificity of 100%. Recently, there has been a significant increase in the proportion of cases diagnosed by the urinary antigen test. The test format is an EIA. It is only specific for *L pneumophila* serogroup 1, which causes the vast majority of LD cases from the community. The average sensitivity of this test is in the range of 70% to 80%.[12] Deoxyribonucleic acid (DNA) amplification by PCR using swab specimens, BAL, urine, and serum[13] enables the specific amplification of minute amounts of *Legionella* DNA and can provide results within a short time frame. It also has the potential to detect infections caused by any *Legionella* species and serogroups.

The effective treatment of LD is based, in part, on the intracellular concentration of antibiotics. Erythromycin, with or without rifampicin, was considered an effective therapy many years ago. Azithromycin, clarithromycin, and the quinolones have replaced erythromycin as a therapy for patients with LD.[14] Usually, 7 to 14 days of therapy is sufficient to cure most patients. However, the therapy duration may need to be considerably longer for patients with lung abscesses, empyema, endocarditis, or extrathoracic infection.

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Life-saving percutaneous intervention in young patient with massive pulmonary embolism

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Massive pulmonary embolism (PE) is not an uncommon condition, and it usually carries a high risk of mortality. It is one of the fatal conditions that commonly affect young patients. A definitive treatment for patients with massive PE is still lacking, and surgical intervention carries a substantial mortality risk. Thus, percutaneous intervention (clot fragmentation and/or aspiration) remains an option in some patients, specifically in those with a risk of bleeding, contraindicating the use of thrombolysis. There have been no randomized trials to validate percutaneous intervention in massive PE. A sufficient level of evidence is still lacking, and its use depends upon the expert committee's opinion and study of previous case reports. We present a 23-year-old man with first onset massive PE secondary to protein C deficiency, who was treated successfully with the combination of systemic thrombolysis and percutaneous interventions.

Pulmonary embolism (PE) is a common, serious and potentially fatal disease. The most severe form of PE, which is massive PE, accounts for about 5% of cases, and is defined by the presence of a large central PE with hypotension, with a systolic blood pressure of <90 mm Hg. It carries a high mortality rate, estimated between 17.4% and 28%, particularly during the first few hours after admission.[1,2] It is believed that the mortality is caused by acute severe right heart failure resulting in cardiogenic shock. Despite this high mortality rate, the treatment of major PE has not been well standardized and remains controversial and elusive. Several modalities of treatment have been implemented upon treating massive PE in particular. Both the British Thoracic Society and the American College of Chest Physicians have developed guidelines that systemic thrombolysis is the mainstay of treatment in massive PE.[3] However, in the event that thrombolysis is contraindicated, one can consider thrombectomy via surgery or percutaneous intervention, depending on the local settings, as there is no head-to-head study that compares the two methods.

CASE

A 23-year-old nursing student, presented to our emergency department with a 3 day-history of worsening of shortness of breath and hemoptysis. He had been well until 1 month earlier when he developed a mild shortness of breath on regular activities associated with cough and minimal hemoptysis. He did not seek medical help until 2 weeks prior when he was diagnosed with pneumonia and treated with oral antibiotics at an outpatient clinic. On completing the antibiotics, the patient reported worsening of the symptoms. On the morning prior of the presentation, the shortness of breath suddenly became intolerable, and he reported of difficulty in talking, associated with pleuritic chest pain. He also had coughed out more fresh blood along with some blood clots. He was then brought to this center by ambulance.

He gave no history of any previous medical illness or pulmonary tuberculosis. He also claimed to have normal appetite and had maintained his weight quite reasonably. On arrival at the emergency department, his vitals were as follows: temperature was 37.2°C; the pulse rate was 156 beats per minute, regular; the respiratory rate was 50 breaths per minute; and the blood pressure was 82/50 mm Hg. Oxygen saturation was only 85% on air. On examination, his breathing was shallow because of chest pain. The lungs revealed coarse crackles over the left lower zone, with no heart murmurs. The rest of the extremities appeared normal.

Arterial blood gases, while the patient was breathing on the high flow mask of 15 L oxygen, revealed severe hypoxemia with the pH of 7.39 (normal blood pH, 7.35-7.50); oxygen partial pressure (PaO_2) of 64 mm Hg (normal values PaO_2 80-100 mm Hg); carbon dioxide partial pressure ($PaCO_2$) of 40 mm Hg (normal values $PaCO_2$ 35-45 mm Hg) and a bicarbonate level of 24 mmol/L. Because of severe respiratory failure, he was mechanically ventilated in the emergency department. The electrocardiography (**Figure 1**) revealed sinus tachycardia, right bundle branch block, and an S1Q3T3 pattern. The chest radiograph (**Figure 2**) revealed a wedge-shaped opacity in the left lower lobe, which is a finding of pulmonary infarction (Hampton hump) at the left lung.

His CT pulmonary angiogram (**Figure 3**) demonstrated a large thrombus in the right main pulmonary artery (PA). A thrombus was also seen in the proximal left descending artery with a segment of the left lower lobe consistent with pulmonary infarction. The diagnosis of massive PE was made. Surgical services were unavailable at the time of embolectomy, and because of the presence of a contraindication to thrombolysis (hemoptysis), we decided to bring him to the cardiac invasive laboratory. In the cardiac invasive laboratory, a right femoral vein puncture was made and a 14-F myelin sheath was inserted. Using a Cournand catheter, a 0.035 guidewire was inserted into the main PA; the catheter was then changed to a pigtail catheter. The PA pressure was recorded (as shown in **Figure 4**) as 62/35 mm Hg (normal, 8-20 mm Hg) and the systemic pressure as 75/40 mm Hg.

The right and left pulmonary angiograms were performed and shown in **Figures 5 and 6**, respectively. The right pulmonary angiogram showed a huge filling defect, obliterating the distal main right pulmonary trunk. Likewise, the left pulmonary angiogram showed a filling defect in the lower left artery.

Then, a 14-F myelin sheath was inserted into the main PA for support. A Balloon OPTA PRO 7×14 mm (Cordis Corporation, Bridgewater, NJ, United States) (**Figure 7**) was inflated to compress and passed through the thrombus several times (clot fragmentation). The result is shown in **Figure 8**. A significant amount of thrombus was still visible; however, the

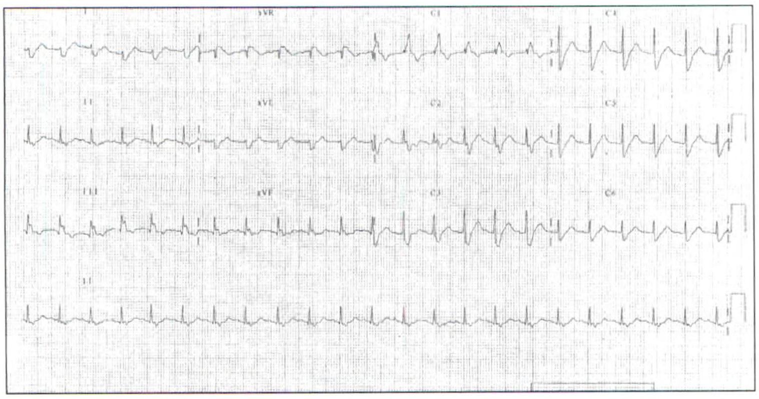

Figure 1. Electrocardiography of the patient in the case report showing sinus tachycardia, right bundle branch block and S1Q3T3 pattern.

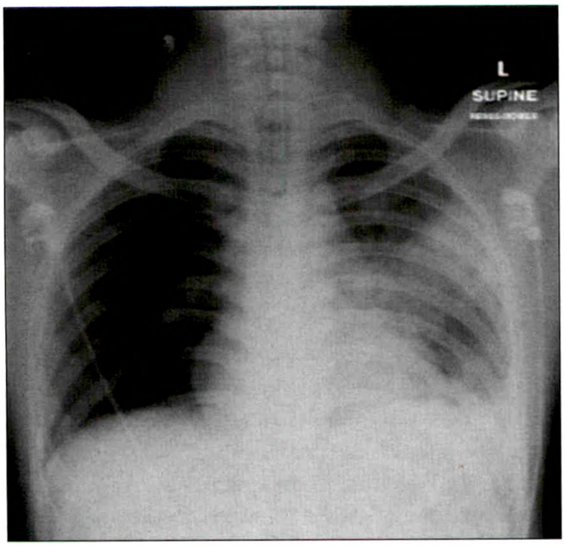

Figure 2. Chest radiograph of the patient in the case report revealing a wedge-shaped opacity in the left lower lobe which is a finding of pulmonary infarction (Hampton hump) at the left lung.

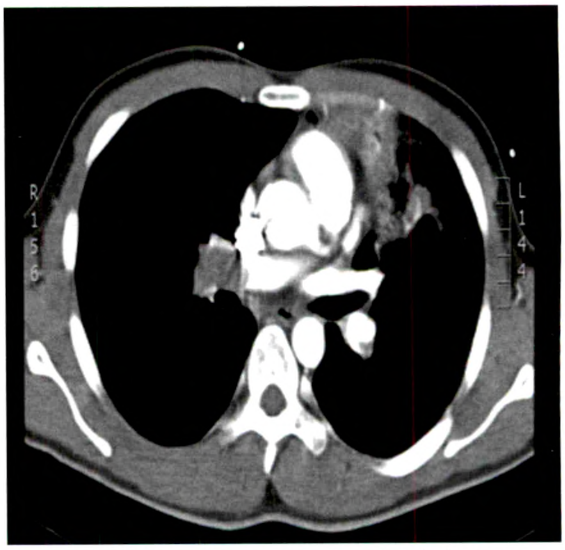

Figure 3. CT pulmonary angiogram of the patient in the case report revealing a large thrombus in the right main pulmonary artery.

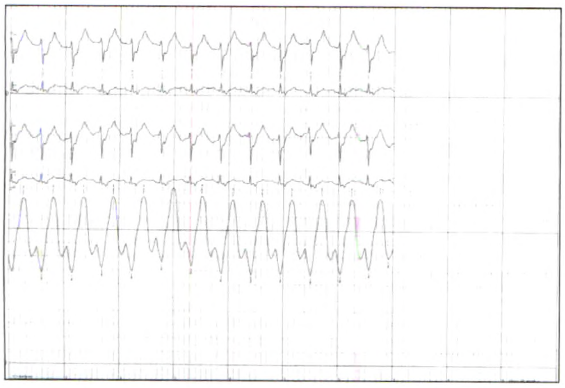

Figure 4. Pressure tracing of pulmonary artery with pressure recorded as 62/35 mm Hg.

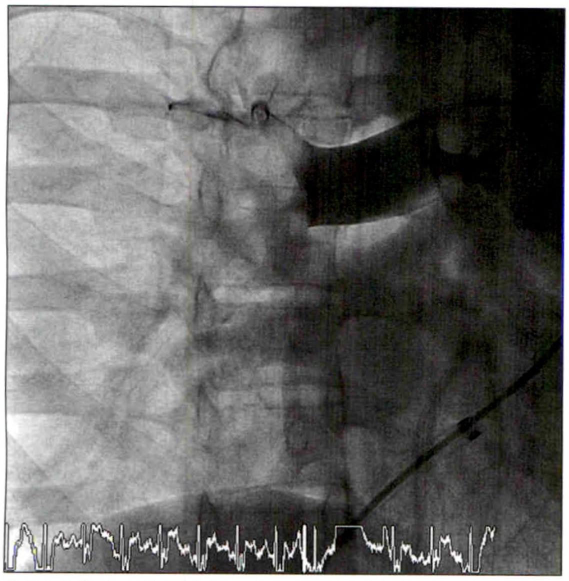

Figure 5. Right pulmonary angiogram showing huge filling defect obliterating the distal main right pulmonary trunk.

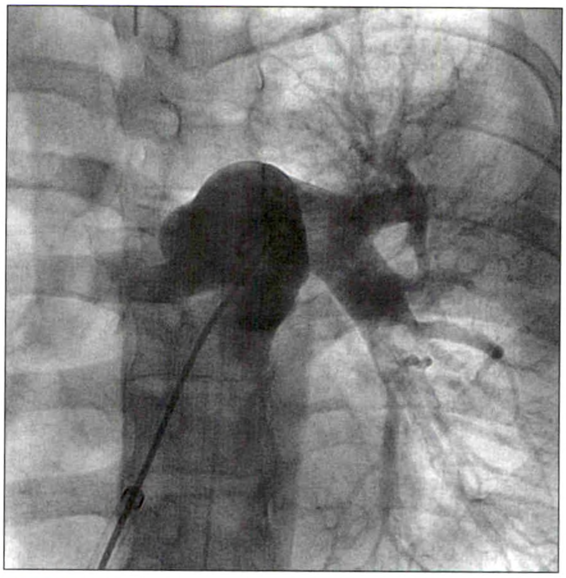

Figure 6. Left pulmonary angiogram showing a filling defect in the lower left artery.

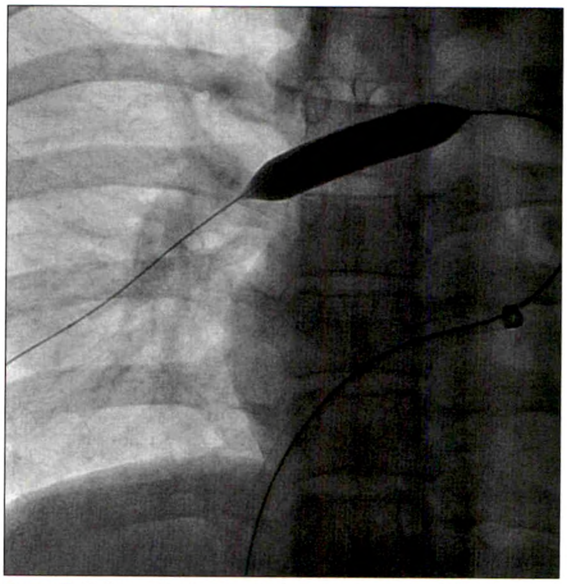

Figure 7. Balloon clot fragmentation done with OPTA PRO 7×14 mm (The balloon was inflated to compress and passed through the thrombus a several times).

acute occlusion was relieved, and a much improved blood flow could be appreciated in the right pulmonary arterial system.

After the procedure, the patient was transferred to the cardiac care unit (CCU). He was then started on intravenous streptokinase 1.5 MU over 1 hour in the CCU for 2 days. We did not adopt the standard regimen of continuous infusion of streptokinase because of the high risk of bleeding. On day 3, hemodynamic parameters were still unchanged as the patient still needed maximal inotropic support. His echocardiogram showed a very dilated and hypokinetic right ventricular chamber with an elevated pulmonary systolic pressure of 50 mm Hg (normal, 8-20 mm Hg); the left ventricle ejection fraction was 70%, and no pericardial effusion was noted. We decided to repeat the pulmonary angiogram (**Figure 9**). It showed some small residual thrombus in the right PA, but much improved blood flow compared to that previously recorded. However, we had given 50 mg recombinant tissue plasminogen activator bolus intrapulmonary during this procedure. The patient then made a steady recovery over the next 7 days. He was extubated on the 10th day of admission. The thrombophilia study confirmed the protein C deficiency, and he was commenced on

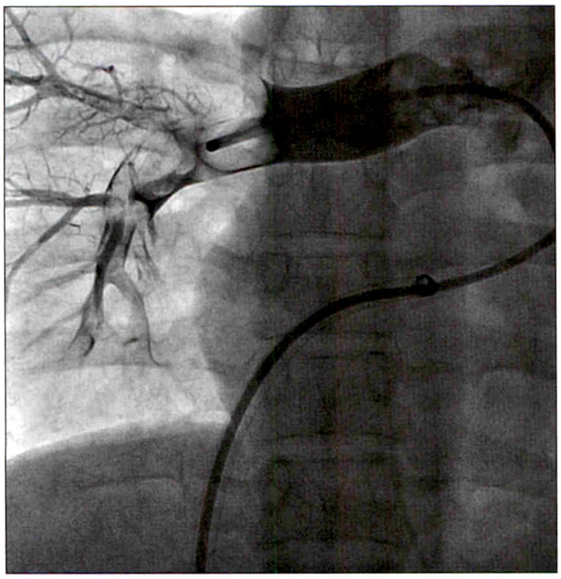

Figure 8. Result after clot fragmentation with Balloon OPTA PRO 7×14 mm, showing a significant amount of thrombus, but much improved blood flow in the right pulmonary arterial system with relief in acute occlusion.

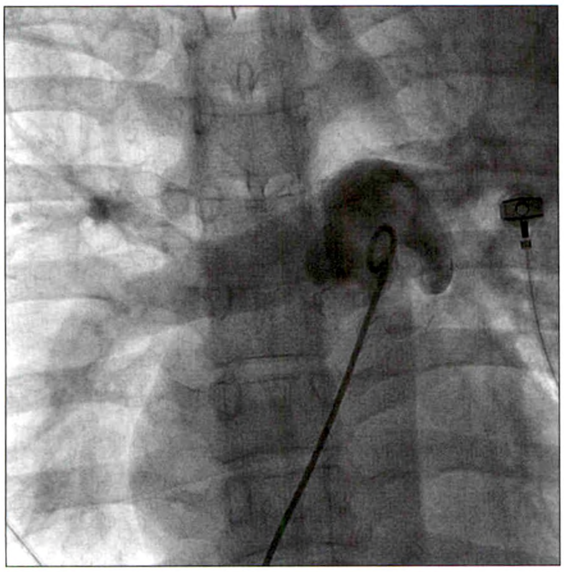

Figure 9. A repeat pulmonary angiogram showing small residual thrombus in the right pulmonary artery

lifelong warfarin. The patient was discharged on the 14th day and last seen in clinic in August 2010. Screening of the family members was arranged in the outpatient clinic.

DISCUSSION

The aim of treatment in massive PE is to relieve the acute right heart failure by lysing or fragmentizing the thrombus, thus restoring cardiac and pulmonary functions. In the presence of contraindication to thrombolysis because of the bleeding risk, surgical or percutaneous interventions have been advocated. To date there is no evidence in the form of randomized controlled trials to compare these two modalities. Arguably, one may advocate thrombolysis with tissue plasminogen activator (tPA) as the best treatment for this patient, as hemoptysis is not an absolute contraindication to thrombolysis. However, tPA is not readily available in our hospital and needs to be ordered from the company, which could certainly result in a significant delay of definitive treatment. Furthermore, transfer to the cathlab was not an issue in terms of delaying the treatment, since the patient presented during working hours and the cathlab was readily available at the time.

The mortality in massive PE is largely contributed by the acute right heart failure. Thus, one can improve survival chances by relieving the pulmonary arterial obstruction. In this patient, during the second angiogram, the burden of the thrombus had already been significantly reduced, and that was before tPA administration. The tPA was given anyway with the intention to lyse whatever residual thrombus that might still be present at the time.

This case illustrated the success of percutaneous thrombus fragmentation using balloon, combined with systemic and intrapulmonary thrombolysis. This technique is potentially life saving when thrombolysis is contraindicated, and especially in peripheral centers where surgical services are not available.

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Re: Glycogen hepatopathy in a 13-year-old male with type 1 diabetes

To the Editor: Great thanks are due to Aljabri et al[1] for expanding pediatricians' alertness on the glycogen hepatopathy in children with type 1 diabetes mellitus (T1DM). Though the studied patient had a 3-year history of T1DM, it should be noted that hepatic glycogenosis could occur at any stage of T1DM and might even be one of its earliest manifestations, together with those classically reported at the onset of T1DM. Since long-standing hyperglycemia and overinsulinisation are metabolic prerequisites for hepatic glycogen storage, liver glycogenosis should be expected to be not uncommon during the first phases of T1DM, especially in the cases that are initially treated with supraphysiological insulin doses.[2] Also, it should be noted that the studied patient needs to be kept under regular follow-up as recurrent hepatomegaly and elevated transaminases are not uncommon. Should recurrence occur, genetic analysis of the liver glycogen phosphorylase gene is suggested.[3]

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Reply to: RE: Glycogen hepatopathy in a 13-year-old male with type 1 diabetes

We thank Prof. Al-Mendalawi for his valuable comments. Glycogen hepatopathy can occur anytime during the duration of diabetes in type 1 diabetes mellitus.

T1DM-associated GH results from excess accumulation of glycogen in hepatocytes, frequently seen in unstable diabetic patients, where hyperglycemia is treated with supra-physiologic doses of insulin. Blood glucose passively enters the hepatocytes in which glycogen synthesis is promoted by high cytoplasmic glucose concentration reliant on the presence of insulin. Glycogen is then trapped within the hepatocytes as a result of a vicious cycle of hyperglycemia and insulin treatment.[1,2]

Diabetic patients with hepatomegaly and abnormal liver enzymes have often been assumed to have NASH rather than GH. A liver ultrasound is not helpful in distinguishing NASH from GH. Consequently, the condition often goes under-recognized with no further evaluation. GH is a liver condition with minor chance or no risk of progression to fibrosis and is reversible with euglycemic control.[1,3]

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Ruptured intracranial dermoid cyst

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A 30-year-old female was referred for symptoms of severe headache for the past 4 days. She had no significant medical history. On examination, she was conscious and oriented, afebrile and her vital signs were within normal limits.

Dermoid cysts are ectodermal inclusion cysts. These lesions have a thick viscous fluid that contains fat and cholesterol. Intracranial dermoid cysts are rare lesions accounting for approximately 0.04-0.6% of all primary intracranial neoplasms.[1] They are slow growing, benign, congenital neoplasms that are commonly seen in the midline, along the parasellar cisterns, and in the fronto-basal and posterior fossa locations. They usually become symptomatic in the third decade. Seizures and headache are the most common symptoms. There is a mild male predominance.[1]

Rupture of an intracranial dermoid cyst is rare and mostly spontaneous, or may occur iatrogenically during surgery or following head trauma.[2] The contents of the ruptured cyst spread into the ventricles and along the subarachnoid spaces inciting severe meningeal inflammation. This results in chemical meningitis, seizures, vasospasm with infarction and death.[1] The incidence of chemical meningitis in ruptured dermoid cysts has been reported to be 7%.[2]

On imaging, ruptured dermoid cysts have a dramatic CT and MR appearance. Plain CT show low-density fat

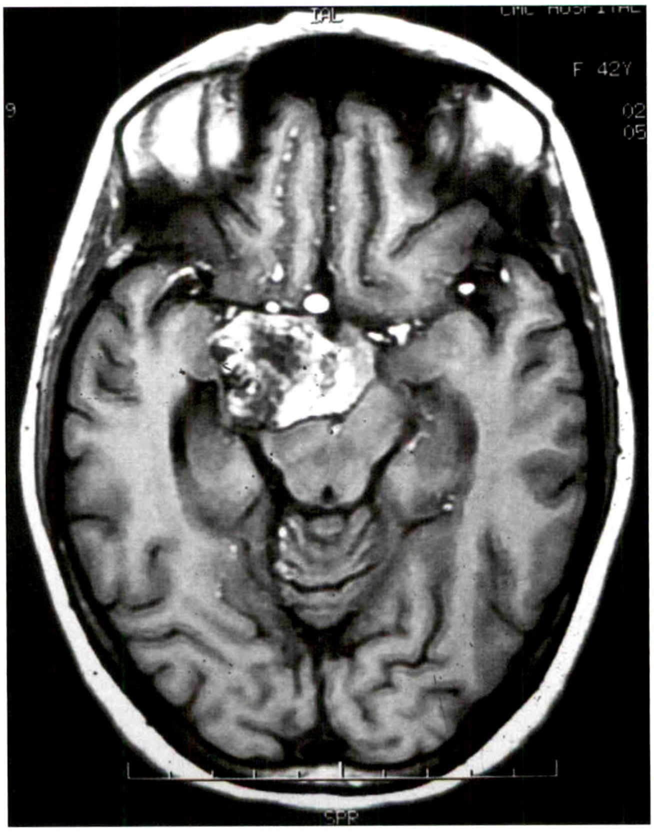

Figure 1. Axial T1 weighted MR image shows a heterogeneously hyperintense mass in the midline/ right suprasellar location, compressing the right cerebral peduncle with multiple small hyperintense foci seen scattered in the subarachnoid spaces.

droplets in the subarachnoid spaces or in the ventricles with intraventricular fat-CSF levels. There is no enhancement on post-contrast studies. In our patient on MRI, ruptured dermoid cysts showed high-signal fat droplets in the subarachnoid spaces and intraventricular fat-CSF levels on both T1 and T2-weighted images (**Figure 1, 2**).

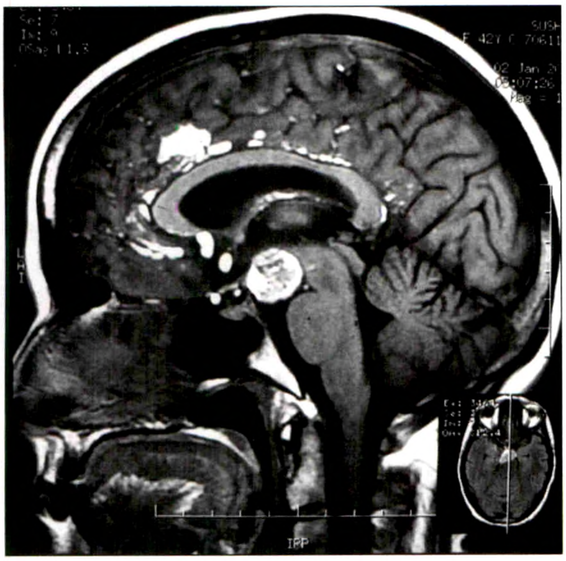

Figure 2. Sagittal T1 weighted MR image shows a heterogeneously hyperintense mass in the midline with multiple hyperintense foci scattered in the subarachnoid spaces and along the corpus callosum.

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for authors and reviewers

EQUATOR
EQUATOR <http://www.equator-network.org> (Enhancing the QUAlity of Trials and Other Research)
The EQUATOR Network seeks to improve the quality of scientific publications by promoting transparent and accurate reporting of health research. The EQUATOR site has links to the following guidelines as well as others.

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STROBE **(STrengthening the Reporting of OBservational studies in Epidemiology)** is an international, collaborative initiative of epidemiologists, methodologists, statisticians, researchers and editors involved in the conduct and dissemination of observational studies.

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The STARD **(Standards for Reporting of Diagnostic Accuracy)** initiative aims to improve the accuracy and completeness of reporting of studies of diagnostic accuracy in order to allow readers to assess the potential for bias in a study and to evaluate the generalisability of its results.

nomenclature for human genes

Please use the guidelines developed by the Human Gene Organization (HUGO) nomenclature committee for human genes:

Human genes
Use approved gene symbols obtained from the HUGO Nomenclature Committee (*http://www.genenames.org/*). Another useful reference is the AMA Manual of Style, Section 15.6.2 Human Gene Nomenclature (*http://www.amamanualofstyle.com*)

Human genetic variation
Designation of single nucleotide polymorphisms (SNPs), deletions, insertions and other gene mutations should follow the guidelines given in Hum Genet 2001; 109:121–124 (*http://www.springerlink.com/content/20y8jygwcyewmf5a/*).

Human cytogenics
Use ISCN nomenclature for cytogenetics notation: Schaffer LG, Slovak ML, Campbell LJ. ISCN 2009: An International System for Human Cytogenetic Nomenclature (2009): Recommendations of the International Standing Committee on Human Cytogenetic Nomenclature. S. Karger AG (Switzerland);2009.

Mouse strain and genetic nomenclature: International Committee on Standardised Genetic Nomenclature for Mice (*http://www.informatics.jax.org/*) new symbols and names for genes should be obtained before submission.

Human gene names and loci should be written in uppercase italics and Arabic numerals. Protein products are not italicized.

Adapted from Guidance for Authors on the Preparation and Submission of Manuscripts to Pharmacogenetics and Genomics

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تطور البلوغ لدى الأطفال والمراهقين المصابين بأمراض مزمنة

الخلفية والأهداف: أعداد متزايدة من الأطفال المصابين بأمراض مزمنة ينجون ويصلون مرحلة المراهقة والبلوغ نظراً لتقدم الرعاية الصحية، ويُعرف عن الحالات الصحية المزمنة أنها تؤثر في نمو الأطفال بما في ذلك النمو الجنسي. وبالرغم من انتشار الأمراض المزمنة في المملكة العربية السعودية، إلا أنه لا توجد دراسات حول بداية سن البلوغ وعلاقته بالأمراض المزمنة، وقد سعت هذه الدراسة إلى استكشاف سن البلوغ بين الأطفال والمراهقين السعوديين الذين يعانون من أمراض مزمنة.

التصميم والمكان: دراسة عرضية أجريت على بعض المدارس بالرياض في المملكة العربية السعودية.

المرضى والطرق: قمنا بالكشف على الطلبة الذين أفاد ذويهم أنهم يعانون من مرض مزمن أو يتناولون أدوية بعيدة المدى، وذلك من أجل تحديد معدل النضوج الجنسي ومعاملات النمو.

النتائج: من بين ١٣٧١ طالباً شاركوا في الدراسة، عانى ١٥٥ (١١,٣٪) منهم من مرض مزمن، كان عدد الذكور ٧٩ (٥١٪)، وكان متوسط الانحراف المعياري لسن الطلبة جميعاً ١١,٤ (٢,٤ سنة). كان ٩٠ طالباً (٥٨٪) يتناولون أدوية لحالاتهم الصحية، كان الربو القصبي هو أكثر الأمراض المزمنة شيوعاً (العدد= ٦٦، ٤٢,٦٪)، تلاه اضطرابات الدم (العدد= ٤١، ٢٦,٥٪). ظهرت السمنة أو زيادة الوزن عند ٥٣ (٣٤٪) من الطلبة، وبالنسبة لنمو القند عند الذكور، كان متوسط عمر الأولاد في مرحلة القند ٢: ١١,٧ عاماً والمرحلة ٣: ١٣,٥ عاماً والمرحلة ٤: ١٤,١ عاماً والمرحلة ٥: ١٤,٦ عاماً، وبالنسبة لنمو الثدي عند الإناث، كان متوسط عمر البنات في المرحلة ٢: ١٠,٧ أعوام والمرحلة ٣: ١١,٣ عاماً والمرحلة ٤: ١٢,٤ عاماً والمرحلة ٥: ١٤,١ عاماً، وكان نمو شعر العانة عند الأولاد والبنات مماثلاً لنمو القند أو الثدي على التوالي.

الاستنتاج: بداية سن البلوغ عند الأولاد والبنات الذين يعانون من أمراض مزمنة هي ضمن الحدود الطبيعية، وربما يساهم ارتفاع معدل السمنة وزيادة الوزن في هذه الظاهرة، ولكن تبقى هناك حاجة لمزيد من الدراسات التي تأخذ بعين الاعتبار تأثيرات المرض المزمن وشدته واستخدام الأدوية باعتبارها عوامل مساهمة.

نمط تفاعلية اختبار الرقعة لدى المرضى المشخصين سريريا ب "التهاب الجلد التماسي" دراسة في مستشفى

مقدمة والأهداف: ترتبط الحساسية التماسية بمراضة مهمة في جميع أنحاء العالم. أجريت هذه الدراسة لاستقصاء نمط التحسيس بمسببات الحساسية التماسية لدى السكان المحليين.

التصميم والمكان: أجريت دراسة استعادية لاستقصاء تفاعلية اختبار الرقعة لدى المرضى الذين تم تشخيص حالاتهم سريريا بأنها التهاب الجلد التماسي والذين أحيلوا إلى عيادة الحساسية في مستشفى الملك خالد الجامعي في الرياض بين إبريل ٢٠٠٨م ومارس ٢٠١٠م.

المرضى والطرق: من أصل ١٩٦ مريضا أحيلوا إلى عيادة الحساسية خلال فترة سنتين تفاعل ٩١ (٪٤٦,٤) منهم مع واحد أو أكثر من مسببات الحساسية لاختبار الرقعة. وتم إشراك هؤلاء المرضى في هذه الدراسة. ضمت مجموعة الدراسة ٨٢ مريضا (٪٩١,١) من الجنسية السعودية و٩ مرضى (٪٨,٩) من جنسيات أخرى. أجري اختبار الرقعة باستخدام فحص T.R.U.E الذي يحتوى على ٢٤ مسببا/خلائط مسببات.

النتائج: من أصل ٩١ حالة تفاعلت إيجابيا مع مسبب واحد أو أكثر كان ٦٧ (٪٧٣,٦) منها إناث متوسط أعمارهن ٣٧ (٨,٣ سنة) و٢٤ (٪٢٦,٤) ذكرا متوسط أعمارهم ٣٤ (١١,٦سنة). تفاعل ثلاثة وثلاثون (٪٣٦,٢) مريضا مع سلفات النيكل و١٤ (٪١٥,٣) مع بي-فينيلينديامين و١٣ (٪١٤,٢) مع راتين بي-تيرت-بوتيلفينول-فورمالديهايد و١٣ (٪١٤,٢) مع ثايمروسال و٩ (٪٩,٨) مع كولوفوني. أما التفاعلية مع باقي المسببات فلم يكن فيها ما يلفت الانتباه. تفاعلت نسبة أعلى بدرجة مهمة من الإناث مع سلفات النيكل (٪٨٤,٨ مقابل ٪١٥,٢ من الذكور، P=٠,٠٠٠١)، ومع راتين بي-تيرت-بوتيلفينول-فورمالديهايد (٪٩٢,٣ مقابل ٪٧,٧، P=٠,٠٠٠١) ومع ثايمروسال (٪٧٦,٩ مقابل ٪٢٣,١، P=٠,٠٣).

الاستنتاج: كانت تفاعلية اختبار الرقعة مع سلفات النيكل مرتفعة. يشير نمط الحساسية التماسية الملاحظ في هذه الدراسة إلى الحاجة لإجراء استقصاءات واسعة النطاق للتعرف على المسببات المحلية المسئولة عن الحساسية التماسية ولصياغة سياسات لتجنب التعرض.

نوعية الحياة المرتبطة بالصحة لمرضى التهاب الكبد ب و ج السعوديين

المقدمة والأهداف: بالرغم من أن مرضى التهاب الكبد ج المزمن لا يعانون في الغالب من أعراض إلا أن الكثيرين منهم يعانون من تظاهرات خارج الكبد وتتأثر سلبا نوعية حياتهم المرتبطة بالصحة في حين أن مرضى فيروس التهاب الكبد ب تكون نوعية حياتهم طبيعية أو طبيعية تقريبا. الهدف من هذه الدراسة هو استقصاء نوعية الحياة المرتبطة بالصحة لدى المرضى السعوديين المصابين بفيروس التهاب الكبد ج بالمقارنة مع المصابين بفيروس التهاب الكبد ب في محاولة لتوثيق الانتشار واكتشاف العوامل المرتبطة بتدني نوعية الحياة لهؤلاء المرضى.

التصميم والمكان: هذه دراسة استشرافية ضمت المرضى الذين راجعوا عيادة علاج متخصص لأمراض الكبد في الرياض خلال الفترة من فبراير إلى يوليو ٢٠٠٨م.

المرضى والطرق: طُلب من مرضى متتالين تأكد تشخيصهم بالتهاب الكبد ج والتهاب الكبد ب تعبئة الاستبيان SF-٣٦ ، وتم جمع معلومات عن المعالم الوبائية والتعليمية والاقتصادية والاجتماعية. وتسجيل جميع البيانات السريرية والمخبرية وما توفر من بيانات نسيجية.

النتائج: استوفى مائتان وعشرون مريضا (التهاب الكبد ب ١٠٧ والتهاب الكبد ج ١١٣) معايير الإدراج في الدراسة وشاركوا فيها. وعموما ٤٥٪ منهم كانوا رجالا. وبلغ متوسط العمر ٤١٫٦ (١٨٫١) سنة. حقق مرضى التهاب الكبد ج نقاطا أقل بدرجة مهمة في ”الأداء الجسماني“ . و”محدودية الدور الناتج عن الأداء الجسماني“. و”الأداء الاجتماعي“. و”الألم الجسماني“. لم نلحظ فروقا مهمة في المعالم الأخرى التي تمت ملاحظتها. تم دراسة ترابط متغيرات وبائية ومختبرية مختلفة مع أجزاء مختلفة من استبيان نوعية الحياة HRQOL.

الاستنتاج: حقق مرضى التهاب الكبد ج السعوديون نقاطا أقل بصورة هامة في أجزاء مختلفة من استبيان نوعية الحياة HRQOL مقارنة مع مرضى التهاب الكبد ب.

العلاقة بين نتائج فحص تحدي الجلوكوز في الحالات ذات المستويات العالية من الجلوكوز ومعدلات سكر الحمل وخلل تحمل الجلوكوز خلال فترة الحمل

الخلفية والأهداف: بالرغم من أن فحص تحدي الجلوكوز (٥٠غم) هو الأكثر استخداماً لفرز حالات سكر الحمل إلا أنه لا يوجد إجماع على طريقة تشخيصية للمريضات اللاتي تعانين من مستويات عالية من الجلوكوز. وقد كان هدفنا في هذه الدراسة تقدير القيمة التشخيصية لنتائج فحص تحمل الجلوكوز المرتفعة وأثر سن المريضة عن طريق استخدام فحص تحمل الجلوكوز كمعيار مرجعي.

التصميم والمكان: أجريت دراسة استعادية في مستشفى للنساء في أنقرة. وقد شملت الدراسة المريضات اللاتي خضعن لفحص تحدي الجلوكوز خلال الفترة ما بين يناير ٢٠٠٥م وديسمبر ٢٠٠٨م.

المرضى والطرق: شملت هذه الدراسة الاستعادية ٦٢٦ امرأة حبلى ممن خضعن لفحص تحمل الجلوكوز (١٠٠غم) الذي دام ٣ ساعات بعد أن ظهرت نتائج فحص تحدي الجلوكوز وكانت › ١٨٠ ملغ/ديسيلتر. وقد قمنا بحساب القيم التنبؤية الايجابية لكل فئة من فحص تحدي الجلوكوز لتشخيص سكر الحمل وخلل تحمل الجلوكوز خلال فترة الحمل.

النتائج: نتيجة فحص تحدي الجلوكوز التي كانت › ٢٤٠ ملغ/ديسيلتر حصلت على قيمة تنبؤية ايجابية تساوي ١٠٠٪ لتشخيص سكر الحمل. والنتيجة التي كانت › ٢٣٠ ملغ/ديسيلتر حصلت على قيمة تنبؤية ايجابية تساوي ١٠٠٪ لتشخيص سكر الحمل وخلل تحمل الجلوكوز خلال فترة الحمل وذلك وفقاً لمعيار مجموعة بيانات داء السكري الوطنية و معياركاربنتر وكوستان. النتيجة التي كانت › ٢٠٠ ملغ/ديسيلتر حصلت على قيمة تنبؤية ايجابية تساوي ١٠٠٪ لتشخيص سكر الحمل وخلل تحمل الجلوكوز خلال فترة الحمل للاتي في سن ٣٥ وما فوق وفقاً لمعيار كاربنتر وكوستان.

الاستنتاج: نتيجة فحص تحدي الجلوكوز التي تساوي ٢٠٠ ملغ/ديسيلتر هي القيمة المثلى لتشخيص سكر الحمل وخلل تحمل الجلوكوز خلال فترة الحمل للاتي في سن ٣٥ وما فوق ويمكن التخلي عن فحص تحمل الجلوكوز لهذه الفئة. أما قيمة القطع لمن دون سن ٣٥ فهي ٢٣٠ ملغ/ديسيلتر.

العلاقة بين مؤشر شدة انقطاع النفس الانسدادي أثناء النوم ووظيفة البطين الأيسر وحجمه

الخلفية والأهداف: يؤدي انقطاع النفس الانسدادي أثناء النوم OSA إلى زيادة أمراض القلب والأوعية والوفيات الناجمة عنها، بما فيها ارتفاع ضغط الدم الشرياني المتعمم، ومرض الشريان التاجي، واضطرابات النظم والتوصيل القلبي، وقصور القلب، والجلطة. وقد سعينا في دراستنا إلى تقييم حجم البطين الأيسر ومؤشر أداء عضلة القلب MPI لدى مرضى انقطاع النفس الانسدادي أثناء النوم.

التصميم والمكان: دراسة عرضية المقطع أجريت بين مايو ٢٠٠٧م وأغسطس ٢٠٠٩م في أحد مستشفيات الرعاية التخصصية في اسطنبول بتركيا.

المرضى والطرق: أجرينا دراسة النوم وتخطيط صدى القلب أثناء الليل لأربعين شخصاً لا توجد لديهم أية أمراض قلبية أو رئوية أحيلو إلينا بغرض تقييم انقطاع النفس الانسدادي أثناء النوم. تم تصنيف الأشخاص وفقاً لمؤشر انقطاع النفس إلى ضعف التنفس AHI إلى ثلاثة مجموعات وهي: انقطاع النفس الانسدادي الخفيف أثناء النوم (مؤشر انقطاع النفس إلى ضعف التنفس: ٥-١٤/ساعة: n=٧)، وانقطاع النفس الانسدادي المتوسط أثناء النوم (مؤشر انقطاع النفس إلى ضعف التنفس: ١٥-٢٩/ساعة: n=١٣)، وانقطاع النفس الانسدادي الشديد أثناء النوم (مؤشر انقطاع النفس إلى ضعف التنفس: ≥٣٠/ساعة: n=٢٠). قِسنا سمك الحاجز بين البطينين IVS وسمك الجدار الخلفي لعضلة البطين الأيسر LVPW باستخدام التصوير الحركي M-mode بالإضافة إلى قياس كتلة البطين الأيسر LVM ومؤشر كتلة البطين الأيسر LVMI. حسبنا مؤشر أداء عضلة القلب MPI للبطين الأيسر كما يلي: (زمن الانقباض سويّ الحجم + زمن الارتخاء سويّ الحجم)/ زمن التفريغ الأبهري بناءً على تخطيط صدى القلب بجهاز دوبلر.

النتائج: لم نلاحظ أي اختلاف في السن أو كتلة الجسم بين المجموعات، إلا أن مستوى ضغط الدم كان أعلى في حالات انقطاع النفس الانسدادي الشديد أثناء النوم مقارنة بحالات الانقطاع المتوسط والخفيف. ففي حالات الانقطاع الشديد، كان قياس كل من: سمك الحاجز بين البطينين IVS (١١,٦ [١,٧ مليمتر])، وسمك الجدار الخلفي لعضلة البطين الأيسر LVPW (١٠.٧ [١,٧ مليمتر])، وكتلة البطين الأيسر LVM (٢٦٠.٩ [٥٠,٥ جرام])، ومؤشر كتلة البطين الأيسر LVMI (١٢١,٩ [٢١,١ جرام/م٢]) أكبر من قياسها في حالات انقطاع النفس الانسدادي المتوسط أثناء النوم (٤.٩ [١,٣ مليمتر]، ٩.٩ [١,٦ مليمتر]، ١٩٦,٤ [٣٥,٢ جرام]، ٤٩.٧ [١٣,٢ جرام/م٢] على التوالي، وحالات انقطاع النفس الانسدادي الخفيف أثناء النوم (٨.٩ [٢,٤ مليمتر]، ٩.٨ [٢,٠ مليمتر]، ١٨٧,٦ [٦٦,٢ جرام]، ٩٥,٨ [٢٨,٦ جرام/م٢] على التوالي. في حالات انقطاع النفس الانسدادي الشديد أثناء النوم، كان مؤشر أداء عضلة القلب MPI (٨.٠ [٠,٢]) أعلى بكثير منه في حالات الانقطاع الخفيف (٥.٠ [P‹٠,١])، أما في حالات الانقطاع المتوسط فلم يكن الفرق كبيراً (٨.٠ [٠,١]).

الاستنتاج: يعاني مرضى انقطاع النفس الانسدادي أثناء النوم من شذوذات قلبية ظاهرة تسوء باشتداد انقطاع النفس، وربما يمكن الاستفادة من مؤشر أداء عضلة القلب MPI في الدراسات القادمة لانقطاع النفس الانسدادي أثناء النوم كمقياس بديل للنتائج.

العلاقة بين تكلس الشريان الإكليلي والتروية القلبية لدى نساء لا يشتكين من أية أعراض

الخلفية والأهداف: لا تتوفر في المملكة العربية السعودية معلومات عن العلاقة بين تكلس الشريان الإكليلي CAC والتصوير الومضاني للتروية القلبية MPS لدى نساء لا يشتكين من أية أعراض بغرض التحقق من مرض الشريان التاجي CAD دون السريري. كان الهدف الرئيسي من هذه الدراسة هو استقصاء العلاقة بين الإصابة بتكلس الشريان الإكليلي CAC وإقفار عضلة القلب بسبب الإجهاد من خلال التصوير الومضاني لتروية عضلة القلب MPS لدى نساء لا يشتكين من أعراض.

التصميم والمكان: دراسة استعادية وحيدة المركز أجريت على مدى عامين.

المرضى والطرق: تم التصوير الومضاني لتروية عضلة القلب MPS وفحص تكلس الشريان الإكليلي CAC على مدى ثلاثة شهور لمائة وواحد امرأة (متوسط السن [الانحراف المعياري] ٥٦ سنة [١١]) لا تُعرف إصابتهن بمرض الشريان التاجي CAD. قارنّا تكرار الإقفار بحسب التصوير الومضاني لتروية عضلة القلب MPS مع الإصابة من عدمها بتكلس الشريان الإكليلي CAC وعدد عوامل الخطورة المسببة لمرض الشريان التاجي CAD.

النتائج: كان معدل انتشار الإقفار بحسب التصوير الومضاني لتروية عضلة القلب MPS هو ٢٢٪ (١٠١/٢٢). ومن بين ٢٢ مريضة لديها إقفار بحسب التصوير الومضاني لتروية عضلة القلب MPS، كان معدل تكلس الشريان الإكليلي CAC يساوي صفر عند خمس مريضات (٢٣٪). وتراوح من ١ إلى ٢٠٠ عند أربع منهن (١٨٪). وأكثر من ٢٠٠ عند ١٣ مريضة (٥٩٪) (٠,٠٠٠١ P=). وبالمقابل، من بين ٧٩ امرأة ظهرت نتائجهن طبيعية في التصوير الومضاني لتروية عضلة القلب MPS، كان معدل تكلس الشريان الإكليلي CAC يساوي صفر عند ٤٤ منهن (٥٦٪). وتراوح من ١ إلى ٢٠٠ عند ٢٥ منهن (٣٢٪). وأكثر من ٢٠٠ عند ١٠ منهن (١٣٪). أي أن الإصابة بتكلس الشريان الإكليلي CAC أو عدمها كانت أهم عوامل التكهن بنتيجة التصوير الومضاني لتروية عضلة القلب MPS (٠,٠٠٠١ P=).

الاستنتاج: يترافق تكلس الشريان الإكليلي CAC المتوسط إلى الشديد مع وجود إقفار في التصوير الومضاني لتروية عضلة القلب MPS لدى أكثر من ٥٠٪ من النساء اللاتي لا تظهر عليهن أية أعراض مع وجود عاملين أو أكثر من عوامل الخطورة المسببة لمرض الشريان التاجي CAD. نادراً ما تظهر نتائج غير طبيعية للتصوير الومضاني لتروية عضلة القلب عندما يكون معدل تكلس الشريان الإكليلي CAC يساوي صفر. والنتيجة الطبيعية للتصوير الومضاني لتروية عضلة القلب MPS لا تستبعد إصابة ما دون سريرية لمرض الشريان التاجي. وبالتالي من الملائم لدى النساء اللاتي لا يشتكين من أية أعراض استخدام فحص تكلس الشريان الإكليلي كفحص مغربل أولي.

حالات عدم انتظام ضربات القلب البطيني والنتائج المرتبطة في المرضى المنومين الذين يعانون من متلازمة الشرايين الإكليلية الحادة في السعودية: النتائج من سجل المشروع السعودي لتقييم متلازمة الشرايين الإكليلية الحادة (SPACE)

مقدمة: تبين أن معدل الوفيات في المرضى الذين يعانون من متلازمة الشرايين الإكليلية الحادة مع عدم انتظام ضربات القلب البطيني أعلى من المرضى الذين لا يعانون من انتظام ضربات القلب البطيني. ومع ذلك، فإن هناك ندرة في البيانات عن عدم انتظام ضربات القلب البطيني في المرضى الذين يعانون من متلازمة الشرايين الإكليلية الحادة في بلدان الشرق الأوسط.

التصميم والمكان: دراسة استباقية لمرضى يعانون من متلازمة الشرايين الإكليلية الحادة تم تنويمهم في ١٧ مستشفى حكومي بين شهر ديسمبر ٢٠٠٥م وديسمبر ٢٠٠٧م.

المرضى والطرق: تم تصنيف المرضى كمرضى يعانون من عدم انتظام ضربات القلب البطيني إذا أصيبوا برجفان بطيني أو تسرع القلب البطيني أو كلاهما.

النتائج: من بين ٥٠٥٥ مريضاً يعانون من متلازمة الشرايين الإكليلية الحادة والذين تم إلحاقهم في سجل المشروع السعودي لتقييم متلازمة الشرايين الإكليلية الحادة (SPACE)، تم تشخيص ١٦٨ مريضاً (٣,٣٪) بالإصابة بعدم انتظام ضربات القلب البطيني و١٥١ مريض (٩٨,٨٪) حدثت لهم في المستشفى. الأغلبية العظمى (٧٤,٤٪) حدثت لدى المرضى الذين يعانون من إحتشاء عضلة القلب المصحوب بارتفاع مقطع ST. إضافة إلى ذلك، كان الذكور أكثر عرضة من النساء للإصابة بعدم انتظام ضربات القلب البطيني (OR ١,٧; ٩٥٪ CI ١,١-٣)، Killip class ›I (OR ٢,٠; ٩٥٪ CI ١,٣-٣,١) وضغط الدم الانقباضي ‹٩٠ mm Hg (OR ٦,٤; ٩٥٪ CI ٣,٥-١١,٨) كان مرتبطاً بشكل ايجابي مع عدم انتظام ضربات القلب البطيني. أما بالنسبة للمرضى المنومين الذين يعانون من فرط دهون الدم، فقد كانت نسبة تعرضهم للإصابة بعدم انتظام ضربات القلب البطيني أقل (OR ٠,٤٩; ٩٥٪ CI ٠,٣-٠,٧). إن النتائج السلبية داخل المستشفى والتي تتضمن معاودة الاحتشاء العضلي القلبي والصدمة القلبية والقصور القلبي الاحتقاني والنزيف الشديد والسكتة الدماغية، كانت أعلى في المرضى الذين يعانون من عدم انتظام ضربات القلب البطيني (P≤٠,٠١ لكل المتغيرات) وتدل على سوء احتمالات الشفاء. إن معدل الوفيات داخل المستشفى كانت أعلى بشكل ملحوظ في المرضى الذين يعانون من عدم انتظام ضربات القلب البطيني مقارنة بالمرضى الذين لا يعانون من عدم انتظام ضربات القلب البطيني (٢٧٪ vs ٢,٢٪; P=.٠٠١).

الاستنتاج: إن عدم انتظام ضربات القلب البطيني في المرضى السعوديين المنومين في المستشفى ويعانون من متلازمة الشرايين الإكليلية الحادة كان مرتبطاً بشكل ملحوظ مع المعدلات المرتفعة للأحداث السلبية وارتفاع نسبة الوفيات في المستشفى، باستخدام بيانات سجل متطورة مع عدد كبير من المرضى، وثقت دراستنا وللمرة الأولى مدى انتشار وعوامل الخطر لمرض عدم انتظام ضربات القلب البطيني في عدد غير منتقى لمتلازمة الشرايين الإكليلية الحادة.

هل مرضى متلازمة الشرايين الإكليلية الحادة الذين تم تنويمهم في المستشفى خارج ساعات العمل يعالجون بشكل مختلف؟ دراسة تحليلية للمشروع السعودي لتقييم متلازمة الشرايين الإكليلية الحادة (SPACE)

مقدمة: عادة ما يكون هناك إيحاء بأن مرضى متلازمة الشرايين الإكليلية الحادة الذين تم تنويمهم خارج ساعات العمل لديهم نتائج سريرية أسوأ من المرضى الذين تم تنويمهم خلال ساعات العمل العادية. هدفنا مقارنة نتائج المستشفى والعلاج بين مرضى متلازمة الشرايين الإكليلية الحادة الذين تم تنويمهم خارج ساعات العمل والمرضى الذين تم تنويمهم خلال ساعات العمل العادية.

التصميم والمكان: دراسة مراقبة استباقية لمرضى يعانون من متلازمة الشرايين الإكليلية الحادة الملتحقين بالمشروع السعودي لتقييم دراسة متلازمة الشرايين الإكليلية الحادة من شهر ديسمبر ٢٠٠٥م إلى ديسمبر ٢٠٠٧م.

المرضى والطرق: شملت الدراسة مرضى متلازمة الشرايين الإكليلية الحادة الذين توافرت لهم تواريخ وأوقات التنويم. تم تحديد أوقات ساعات العمل العادية خلال أيام الأسبوع، من الساعة ٨ صباحاً -٥ مساءً، خارج ساعات العمل خلال أيام الأسبوع، ٥ مساءً • ٨ صباحاً، إجازات نهاية الأسبوع وأيام عيد الفطر واليوم الوطني.

النتائج: من بين ٢٨٢٥ مريضاً مؤهلاً لهذه الدراسة التحليلية، تم تنويم ١٠١٦ مريضاً (٣٦٪) خلال ساعات العمل العادية و١٨٠٩ مريضاً خارج ساعات العمل. كان المرضى المنومين خارج ساعات العمل أكثر عرضة للإصابة بقصور قلبي واحتشاء عضلة القلب المصحوب بارتفاع مقطع ST ، وتلقي علاج حالٌّ للفِبْرين، ولكنهم أقل عرضة للخضوع لتدخلات إكليلية أولية عبر الجلد، وكان الوقت المتوسط من دخول الباب إلى استخدام البالون في المرضى المنومين خارج ساعات العمل (١٢٢ دقيقة) أطول بشكل ملحوظ من المرضى المنومين خلال ساعات العمل العادية.لم نلاحظ أي اختلافات بين المجموعتين في نتائج المستشفى بما في ذلك حالات الوفيات، ولكن لوحظ ارتفاع معدلات الإصابة بقصور قلبي في المرضى المنومين خارج ساعات العمل (١١,١٪ vs ٧,٢٪, P، ٠.٠١).

الاستنتاج: إن المرضى الذين يعانون من احتشاء عضلة القلب المصاحب لإرتفاع مقطع ST والذين تم تنويمهم خارج ساعات العمل محرومين من سرعة تلقي التدخل الإكليلي الأولي عبر الجلد ولكن ليس من ناحية تلقي العلاج الحالّ للفِبْرين. ينبغي للمستشفيات التي توفر عمليات التدخل الإكليلي الأولي عبر الجلد خارج ساعات العمل أن تجريها في الوقت المناسب على مدار اليوم.

أورام الخلايا الإنتاشية داخل الجمجمة: تجربة مركز وحيد

مقدمة: لا تُعد أورام الخلايا الإنتاشية داخل الجمجمة GCT من الأمراض الشائعة. وقد راجعنا تجربة مركز وحيد لتحديد المُتغيرات التي تُؤثر على نتائج المعالجة.

التصميم والمكان: دراسة استيعادية لمرضى لديهم أورام خلايا إنتاشيه عولجوا في مركز وحيد (مستشفى الملك فيصل التخصصي ومركز الأبحاث) خلال الفترة من مارس ١٩٨٥م إلى ديسمبر ٢٠٠٧م.

المرضى والطرق: تم تسجيل خمسة وسبعون مريضاً بتشخيص أورام الخلايا الإنتاشية داخل الجمجمة في سجل أورام مستشفى الملك فيصل التخصصي ومركز الأبحاث خلال الفترة من عام ١٩٨٥ إلى عام ٢٠٠٧م. تم استبعاد ٧ مرضى مصابون بورم المنطقة الصنوبرية وتم علاجهم كحالات ورم إنتاشي في السنوات الأولى بدون تشخيص الأنسجة. واقتصرت هذه الدراسة الإستطلاعية على المتبقين خمسين مريضاً لديهم تشخيص نسيجي أو باستخدام الواسمات: ٣١ حالة ورم انتاشي و ١٩ حالة أورام خلايا انتاشية غير الإنتاشي NGGCTs.

النتائج: كان معدل ١٠سنوات من معدل البقيا الإجمالي وحالات البقاء المطلق و البقيا الخالية من النكسات ٨٧٪ و ٨٨٪ و ٩٦٪ لمرضى الورم الإنتاشي. مع متوسط متابعة ٤,٥(يتراوح بين ٢ و ٧) سنوات. بالمقارنة مع ٢٦٪ و ٢٩٪ و ٤٦٪ لمرضى NGGCT مع متوسط متابعة ٣(يتراوح بين ١,٥ و ١٣) سنة. لمرضى NGGCT. المُتغيرات الإيجابية المؤثرة في معدل البقيا الإجمالي: أعمار أصغر(١٦‹ y vs ١٦y,P‹ =٠.٠٥) . جرعة إشعاع أعلى (٥٠‹ Gy vs ٥٠ › Gy ;p =٠.٠٣) والتشخيص في السنوات اللاحقة (١٩٩٠‹ vs ١٩٩٠ › P=٠.٠٠٢) .

الاستنتاج: لا بد من إجراء تشخيص الأنسجة في أورام الخلايا الإنتاشية داخل الجمجمة GCT قبل المعالجة باستثناء مرضى الواسمات المرتفعة. في حالات الأورام الإنتاشية قد يكون العلاج الإشعاعي المحلي RT لمرضى M٠ كافياً. تستدعي الحاجة المتابعة لفترة طويلة للتعرف على فائدة المعالجة الكيميائية. أما في حالات أورام الخلايا الإنتاشية غير الإنتاشية NGGCT فإن الجمع بين نماذج المعالجة والعلاج الإشعاعية بجرعة ٥٠ › سنتيغرية يُعد من العناصر الهامة التي تؤثر على النتائج. ويُوصي دائماً بإعادة النظر في خيار الجراحة واستئصال الأورام المتبقية/ العصية.

الأورام الخبيثة الجديدة بعد زراعة الكبد: تجربة مركز واحد

مقدمة: يخضع مرضى زراعة الكبد لتناول أدوية تثبيط المناعة لمدى الحياة مع جميع عواقبها، وقد ساهم تكرار حدوث الأورام الخبيثة لدى زارعي الكبد في توهين الترصد المناعي، وفي هذه الدراسة نعرض تجربتنا عن أورام خبيثة جديدة تم تسجيلها لدى مريضي زراعة كبد من متبرع متوفي وآخر حي.

التصميم والمكان: دراسة استيعابية للمرضى الذين تمت إحالتهم إلى مركز زراعة كبد في الفترة بين أبريل ٢٠٠١م و يناير ٢٠١٠م.

المرضى والطرق: تم تجميع بيانات مختلفة شملت نوع المرض الخبيث والسمات الهيستوباثولوجية والنظام الدوائي المُثبط للمناعة ونجاة المرضى.

النتائج: من بين ٢٤٨ زراعة كبد أُجريت لـ٢٣٨ مريضاً (١٠ منهم للمرة الثانية)، عانى ٨ مرضى (٣,٤٪) من أمراض خبيثة جديدة بعد الزراعة، وقد شملت الأمراض الخبيثة الجديدة الإضطرابات التكاثرية اللمفاوية لمرضى ما بعد الزراعة (PTLD) في ٥ مرضى من كانت نتائجهم إيجابية لفيروس ابشتين بار EBV، وتم علاجهم بنجاح باستخدام العلاج المضاد لوحيد النسيلة anti-CD٢٠، وتخفيض الأدوية المثبطة للمناعة والسيطرة على نشاط الفيروس EBV، سرطان المثانة البولية لدى مريض واحد تمت علاجه بالإستئصال الجراحي الجذري والعلاج الكيميائي إلا أنه توفي نتيجة لإنتشار الورم في العظم والرئتين بعد عام من تشخيص حالته، سرطان بطانة الرحم لدى مريضة واحدة تم علاجها بالإستئصال الجراحي، وورم كابوسي اللحمي لدى مريض واحد تم علاجه بالإستئصال الجراحي وتخفيض الأدوية المثبطة للمناعة.

الاستنتاج: الإضطرابات التكاثرية اللمفاوية PTLD المصاحبة لفيروس EBV هي أكثر الأمراض الخبيثة الجديدة تكراراً بعد زراعة الكبد ويتم علاجها بسهوله من خلال العلاج الكيميائي وتخفيض الأدوية المُثبطة للمناعة.

ارتباط الانترلوكين ٤ (-٥٩٠ T/C) وتعدد أشكال مورثة مستقبل الانترلوكين ٤ (Q٥٥١R A/G) مع العُدّ الشائع

الخلفية والأهداف: يعتبر العُدّ الشائع من الاضطرابات الجلدية المألوفة، ومع أن السبب الرئيسي لهذا المرض لا يزال بحاجة إلى تحديد، إلا أن التعبير الشاذ لمورثات السايتوكين قد يكون عاملاً مساهماً، وقد سعت هذه الدراسة إلى بحث ارتباط تعدد الأشكال لجين أنترلوكين ٤ (IL٤) المشجع وجين أنترلوكين (IL-٤R) المستقبل كمغيرات للإلتهاب مع العُدّ الشائع.

التصميم والمكان: دراسة ضابطة ضمت ٩٥ مصاباً بالعًدّ من العيادات الجلدية التابعة لمستشفى القصيم الجامعي بالقصيم في المملكة العربية السعودية.

المرضى والطرق: قورنت البيانات الخاصة بمرضى العًدّ مع تلك الخاصة بـ ٨٧ فرداً من المجموعة الضابطة من غير الأقارب في نفس المنطقة، تم استنباط ومعالجة جينوم DNA باستعمال فوري لتضخيم سلسلة تفاعل البوليمريز من أجل تحديد الخصائص المتعلقة بمورثات IL-٤ (-٥٩٠ T/C) و IL-٤R (A/C Q٥٥١R).

النتائج: بالمقارنة مع المجموعة الضابطة، لم يُظهر مرضى العُدّ فرقاً مهماً في معدل تكرار النمط الجيني (IL-٤ ٥٩٠ T/C) (p=٨). ولكن كان هناك فرق مرتفع في IL-٤R (Q٥٥١R A/C) (P<٠.٠٠١). كان معدل تكرار طفرة النمط الجيني IL-٤ GG وكذلك أليل IL-٤R G مرتفعاً ارتفاعاً مهماً في حالات العُدّ مقارنة بالمجموعة الضابطة، وعلاوة على ذلك، أظهرت حالات العُدّ تكراراً أكثر ارتفاعاً للأنماط الجينية المشتركة IL-٤R GG — مع IL-٤ — CC,CT,TT.. ولكن لم يلاحظ فرق هام لدى مقارنة المجموعات الفرعية ذات العلاقة بشدة المرض أو الاستجابة للعلاج (P>٠.٠٥).

الاستنتاج: تؤسس هذه الدراسة لوجود علاقة مهمة لتعدد الشكل الجيني لـ(Q٥٥١R A/C) بالاستعداد للإصابة بالعُدّ الشائع عوضاً عن شدة المرض.

تحليل جزيئي لمرض حمّى البحر المتوسط العائلية لدى مجموعة من المرضى الأتراك

مقدمة: حمّى البحر المتوسط العائلية FMF هي اضطراب وراثي جسدي متنح ناجم عن طفرات في جين حمّى البحر المتوسط MEFV المشفِّر لبروتين pyrin. وتنتشر حمّى البحر المتوسط العائلية بشكل خاص بين الأتراك والأرمن واليهود غير الأشكناز والعرب. كان الهدف من هذه الدراسة تحديد تكرار الطفرات الاثنتي عشرة لجين حمّى البحر المتوسط وطيفها عند هؤلاء المرضى وتحديد العلاقة بين النمط الجيني والنمط الظاهري في هذه المجموعة التركية الكبيرة.

التصميم والمكان: تحليل استعادي للمرضى المُحالين إلى عيادة حمّى البحر المتوسط العائلية بغرض تحليل الطفرات بين يناير ٢٠٠٧م ويونيو ٢٠٠٩م.

المرضى والطرق: قمنا بإدراج ٤٤٦ مريضاً تركياً بحمّى البحر المتوسط العائلية وحددنا الطفرات الاثنتي عشرة المعروفة بواسطة الاستقصاءات السريرية. تم تضخيم الدنا DNA بواسطة تفاعل البوليمراز المتسلسل PCR وأخضعناها للتهجين العكسي لاكتشاف طفرات جين حمّى البحر المتوسط.

النتائج: من بين ٤٤٦ مريضاً، وجدنا ١٠٣ (٤٦,٦٪) يحملون نمطاً جينياً متغاير الزيجوت، و٤٤ (١٩,٩٪) لديهم نمط جيني متماثل الزيجوت، و٧٤ (٣٣,٤٩٪) لديهم زيجوت متغاير مركب. وكانت أكثر الطفرات المكتشفة شيوعاً هي الزيجوت المتماثل M٦٩٤V (٢٢١/٤٦). ومن بين ٤٤٦ مريضاً كان عدد الذكور ٢١٨ (٤٨,٨٧٪) والإناث ٢٢٨ (٥١,١٢٪). وقد أثر ارتفاع معدلات القرابة بين الوالدين على تطور حمّى البحر المتوسط العائلية. وتفاوَت الطيف السريري مع أشكال الطفرة المختلفة.

الاستنتاج: تؤدي هذه الدراسة دوراً هاماً في اكتشاف توزيع طفرات جين حمّى البحر المتوسط وتحديد المقاربة السريرية لدى المرضى الأتراك المصابين بحمّى البحر المتوسط العائلية. كما بدا أننا اكتشفنا صورة سريرية مميزة، وهي قلة حدوث الداء النشواني على وجه التحديد.

المدونات الطبية السعودية

تصدر المدونات الطبية السعودية مرة كل شهرين عن مستشفى الملك فيصل التخصصي ومركز الأبحاث ، ص.ب ٣٣٥٤ ، الرياض ١١٢١١، المملكة العربية السعودية. يتم توزيع المدونات وإعداد الملخصات العربية بالتعاون مع د. زهير القاوي بواسطة موظفي إدارة الخدمات الإدارية بمستشفى الملك فيصل التخصّصي ومركز الأبحاث. جميع المراسلات والاستفسارات وطلبات الاشتراك ترسل إلى المحرر الأول مكتب المطبوعات (ر.إ ٣٦).

سعر الاشتراك ١٠٠ ريال في السنة للأفراد داخل المملكة و٢٠٠ ريال في السنة للأفراد خارج المملكة و٥٠٠ ريال في السنة للمؤسسات. يمكن فتح اشتراك مجاني للأفراد و المؤسسات في الدول النامية.

ترسل طلبات الاشتراك أو إلغاء الاشتراك الى البريد الإلكتروني: *admin@annsaudimed.net*

الأراء التي ترد في المقالات المنشورة تعبّر عن رأي أصحابها فقط ولا تعبّر عن وجهة نظر المجلة. جميع الحقوق محفوظة للمجلة الطبية. لا يسمح بإعادة طبع أي جزء من المجلة أو نسخه بأي شكل وبأي وسيلة كانت إليكترونية أو آلية، بما في ذلك التصوير والتسجيل أو الإدخال في أي نظام حفظ أو استعادة معلومات بدون الحصول على موافقة من إدارة المجلة.

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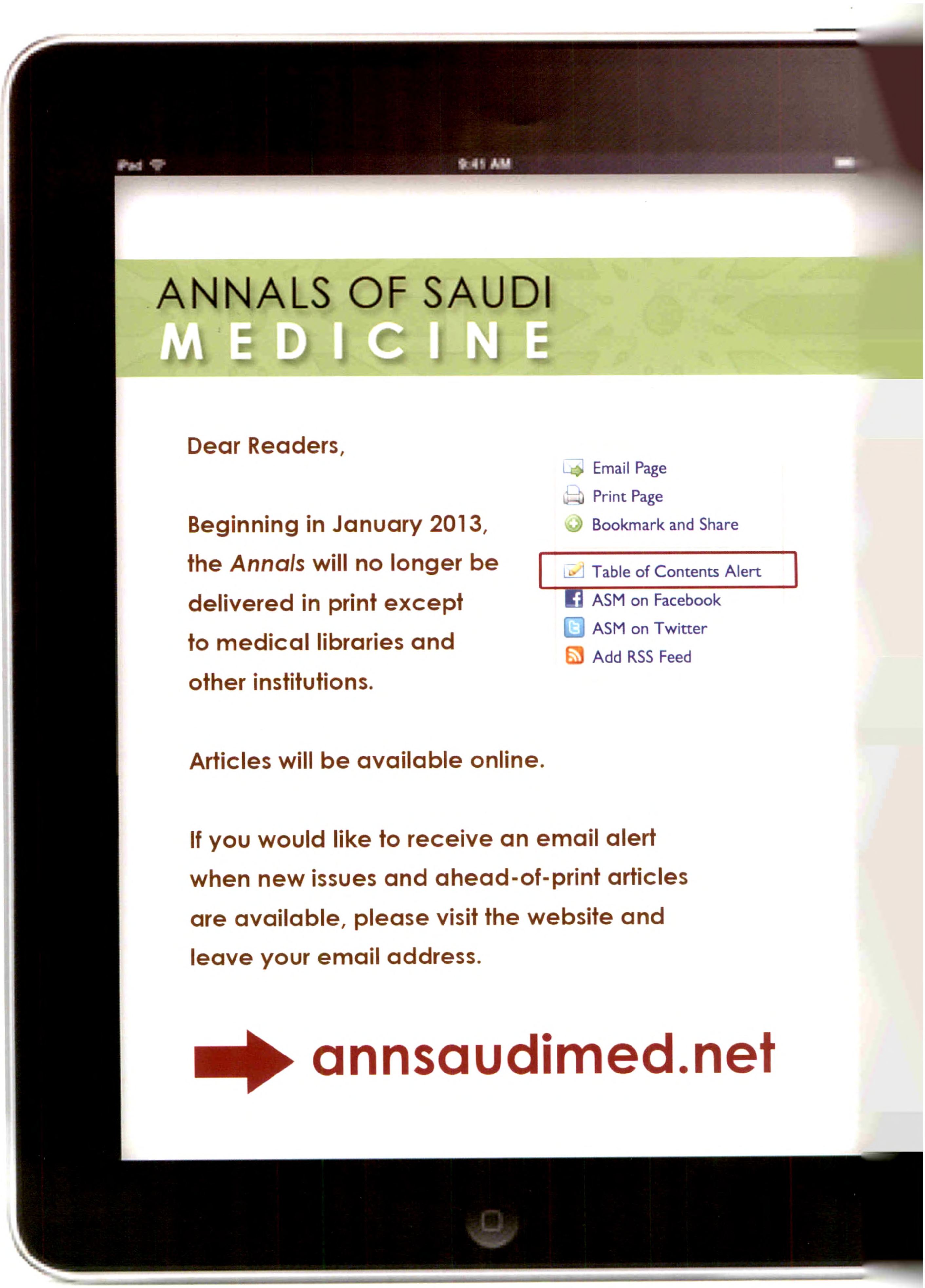

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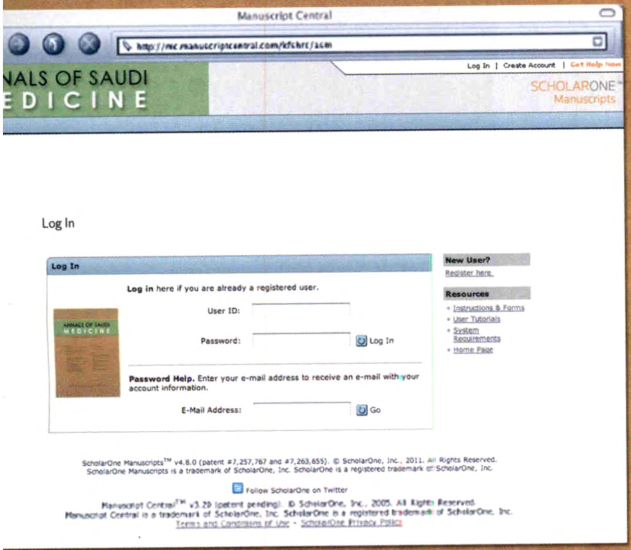

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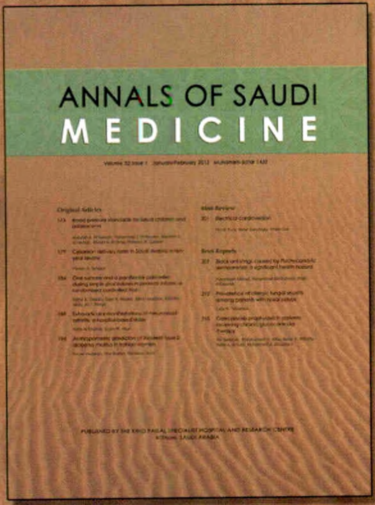

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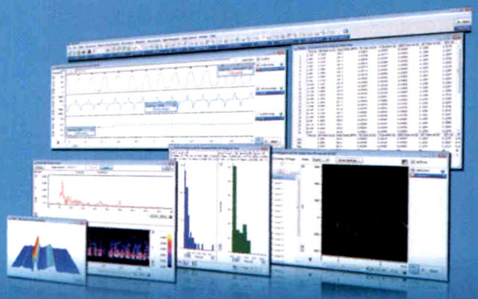

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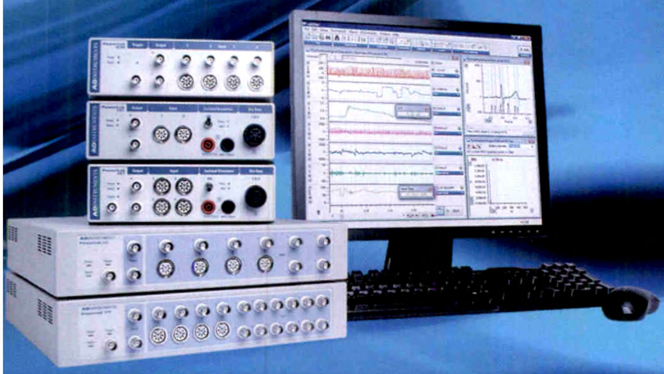

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SUMMARIES

INFECTIOUS DISEASE

Antiretroviral resistance in HIV-infected Saudi children failing first-line highly active antiretroviral therapy

In a retrospective study, Al Hajjar and colleagues found the prevalence of resistance to any ARV drug among 22 children was 86.4%. The best susceptibility was to lopinavir. Inadequate adherence is a common cause for resistance in children. The children in this study responded satisfactorily to genotype-guided treatment and intensive family counseling.

QUALITY OF LIFE

Quality of life in hemodialysis and peritoneal dialysis patients in Saudi Arabia

In a cross-sectional study of hemodialysis and peritoneal dialysis patients, Al Wakeel and colleagues found that QoL mean scores were significantly higher among peritoneal dialysis in all domains and in the total QoL, with the exception of the score of physical QoL. Age, male gender, and dialysis duration were negative predictors of QoL score in a multiple regression analysis.

CARDIOLOGY

Viabahn for femoropopliteal in-stent restenosis

In a retrospective review of records over a 5-year period, Al Shammeri and colleagues found that 1 and 3-year primary favorable patency rates were 85.1% and 81.4%, respectively, in 27 patients treated with the ePTFE-covered Viabahn stent-graft.

Characteristics of Saudi patients with congestive heart failure and adherence to management guidelines in a tertiary hospital in Riyadh

Alqahtani and colleagues analyzed the records of 392 patients with CHF. Hypertension was the predominant comorbid illness followed by diabetes type 2 and hyperlipidemia. Spironolactone, exercise and vaccination were the the least least adhered to recommendations. They encourage physicians to undergo continuing medical education and training courses to properly implement current recommendations in the management of heart failure.

OBSTETRICS AND GYNECOLOGY

Ovarian volume assessment in relation to histologic findings and sex hormone levels in women with postmenopausal bleeding and a thickened endometrium

In a prospective observational study, Elfayomy and El Tarhouny found that large ovaries among 90 women with postmenopausal bleeding and thick endometrium were associated with elevated serum sex steroid hormones. A thickened endometrium was a marker of risk for endometrial adenocarcinoma.

NEPHROLOGY

Chyluria: a mimicker of nephrotic syndrome

In a retrospective review, Kaul and colleagues identified 12 patients misdiagnosed with nephrotic syndrome and treated aggressively with immunosuppression with no benefit who were later diagnosed as having chyluria. Checking the urine for chyle can help identify these patients.

PEDIATRICS

Childhood onset of Crohn disease: experience from a university teaching hospital in Saudi Arabia

In a retrospective study on data collected over nearly a ten-year period, Saadah found that the clinical pattern of Crohn disease in 96 patients in the Western Province was similar to that in children in the West. Physicians should be aware of the varying presentation and make early referrals to specialized centers.

Metabolic syndrome components in obese Egyptian children

In 60 obese and 50 non-obese children, Zaki and colleagues found that obese children showed significantly higher values in waist circumference, waist-to-hip ratio, levels of systolic and diastolic BP, insulin, HOMA-IR and LDL and lower HDL compared to their lean controls. They conclude that the prevalence of metabolic syndrome is frequent among obese Egyptian children.

Chronic recurrent multifocal osteomyelitis: a first report from Saudi Arabia

In ten patients with CRMO referred to their pediatric rheumatology department, Almayouf and colleagues found that the referral diagnosis was inaccurate. Imaging was consistent with chronic osteomyelitis and confirmed in nine patients. CRMO may be overlooked in the community.

FAMILY AND COMMUNITY MEDICINE

Causes of death certification of adults: an exploratory cross-sectional study at a university hospital in Riyadh, Saudi Arabia

Ansary and colleagues reviewed all death certificates issued in 2008. In nearly two-thirds of cases, the first reported cause of death was "inappropriate." They conclude that educational, system-related and legal interventions to improve the accuracy of death certification are strongly needed.

Wilson disease in 71 patients followed for over two decades in a tertiary center in Saudi Arabia: a retrospective review

Peedikayil and colleagues describe the clinical and laboratory findings in the largest cohort of patients reported from the Middle East. They note that Wilson disease should be considered in patients of any age with obscure hepatic and/or neurological abnormalities.

Evaluation of internet use for health information by parents of asthmatic children attending pediatric clinics in Riyadh

AlSaadi collected data on internet use from the parents of 500 asthmatic children. Reasons for internet use were reassurance, clarification, online consulting, and new management schemes. The most important predictors for internet use were higher mother education, followed by higher father education and non-health related mother occupation.

Antiretroviral resistance in HIV-infected Saudi children failing first-line highly active antiretroviral therapy

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BACKGROUND AND OBJECTIVES: The use of a potent combination of antiretroviral (ARV) drugs, so-called highly active ARV therapy (HAART), has dramatically improved the quality of life and overall survival of children with human immunodeficiency virus (HIV) infection. However, these benefits can be compromised by the development of drug resistance. Our objectives were to analyze the prevalence and pattern of HIV-drug resistance among HIV-infected children failing first-line HAART.

DESIGN AND SETTING: Retrospective study based on data obtained from July 2006 through January 2009 of prevalence of genotypic resistance estimated in HAART-treated children who experienced virologic failure (HIV RNA>1000 copies/mL) at a tertiary care center in Riyadh.

PATIENTS AND METHODS: The characteristics of the study population and genotype resistance data were analyzed in ARV-treated children who experience virologic failure.

RESULTS: Among 22 children who underwent resistance testing, the prevalence of resistance to any drug was 86.4%. Inadequate adherence to ARVs in children with drug resistance was 91%. Twenty-four mutations were detected within the protease coding region and 14 in the reverse transcriptase (RT) coding region. In 80% of isolates piM36I was detected, while rtM184V was detected in 70% of the isolates and was associated with cross-resistance to at least two nucleoside RT inhibitors (NRTI). Clinically significant non-nucleoside RT inhibitors (NNRTI) resistance was conferred by rtK103N. The best ARV susceptibility was to lopinavir in the PI class. ARV resistance was not associated with geographic regions or the CDC classification status. Study children responded satisfactorily to genotype-guided treatment and intensive family counseling.

CONCLUSION: ARVs resistance is common among HIV-infected Saudi children who experienced virologic failure to HAART. Inadequate adherence is a common cause for resistance to ARVs in children. Mutations M36I and M184V were more frequent for PIs, NRTIs and NNRTIs. Evaluation of genotype tests should be considered in all children with therapeutic failure to guide future selection of ARV regimens. These data will help improve clinical management of HIV-infected children in Saudi Arabia.

Currently, 2.5 million children are living with HIV/AIDS, of whom more than 90% reside in sub-Saharan Africa. Access to antiretroviral (ARV) agents has increased dramatically over the past years. The number of children under 15 years of age receiving antiretroviral therapy increased by 29% between 2008 and 2009. About 356 400 children less than 15 years of age were receiving ARV therapy in low and middle-income countries at the end of 2009, up from 275 300 at the end of 2008. Children represented 6.8% of people receiving ARV therapy and 8.7% of people in need.[1] The ultimate goal of ARV is to achieve virologic suppression and immune reconstitution. Virologic suppression is defined as a reduction in plasma HIV RNA to below the limit of detection or <50 copies/mL (cpm). Immune reconstitution is reflected by an increase in CD4 positive T cell count. HAART has dramatically improved the quality of life and overall survival of individuals infected with HIV-1. Sub-optimal exposure to ARV can rapidly select the development of resistant mutation. These resistant variants can rapidly emerge and ultimately lead to virologic failure (defined as the inability to achieve virologic suppression within 16 to 24 weeks of initiation of ARVs or persistent HIV RNA load >1000 cpm).[2] In the United States and western Europe, nearly 80% of HIV-1 infected adults who experienced virologic failure harbored virus strains resistant to at least one ARV drug.[3] Few studies on emerging resistant mutations in children were available in selected cohorts of limited size.[3-10]

There are essentially two types of assays for detecting ARV resistance in routine clinical practice. Phenotypic assays measures the susceptibility of the virus to various drugs in a tissue-culture system while genotypic assays detect the presence of resistance mutations. Genotypic assays are most commonly used in clinical practice because they are generally less expensive, laborious and time-consuming than phenotypic assays.[11] The objective of this study was to estimate the prevalence and pattern of ARV resistance in HIV-infected children who failed HAART.

PATIENT AND METHODS

All perinatally HIV-infected children followed in the King Faisal Specialist Hospital and Research Centre comprehensive HIV care program who received triple ARV therapy or highly active ARV therapy (HAART) according to the recommendation of the working group on ARV therapy and medical management of HIV-infected children[12] were included in the analysis. Genotypic resistance tests were performed in patients with virologic failure (defined as plasma HIV RNA >1000 copies/mL) to optimize the choice of new ARV regimens. The blood samples had genotype tests performed using TRUGENE HIV-1 genotyping kit (DNA-sequencing assay, Bayer Healthcare; healthcare.bayer.com) and interpretative results were based on the manufacturer's guideline. The analysis was carried out on data obtained between July 2006 and January 2009.

Table 1. Characteristics of HIV-infected children experiencing therapeutic failure.

Characteristic	
Median age (years)	7
Gender Male Female	 13 (59.1) 9 (40.9)
CDC (Category C)[a]	2 (9.1%)
CDC (AIDS-defining conditions)[a]	2 (9.1%)
Virologic failure[b] and documented resistance	22 (86.4%)
Median CD4 count and range (cells/m³)	817 (134-1885)
Median HIV-RNA viral load and range (copies/mL)	1352 (1100-20 202)
Inadequate adherence to ARVs	20/22 (91%)

Values are number (%) unless otherwise indicated.

[a] The Centers for Disease Control and Prevention (CDC). Clinical categories for children younger than 13 years (Category C= HIV encephalopathy) years and CDC case definition for AIDS-defining conditions: for adolescent and adult, 13 years of age and older (recurrent bacterial pneumonia=3 episodes in 1 year).

[b] Virologic failure: persistent viremia (HIV-RNA viral load >1000 copies/mL).

RESULTS

Among children receiving HAART, the proportion of children who experienced persistent viral load >1000 copies/mL was 48% (22/46). The characteristics of study population are summarized in **Table 1**. Overall, a genotype test was performed at least once in the 22 children who experienced virologic failure. The prevalence of resistance to any ARV drugs was 86.4%. Inadequate adherence to ARVs in children with drug resistance was 91%. Twenty-four mutations were detected within the protease coding region and 14 in the RT coding region (**Tables 2, 3**).

The most common mutation (found in 71% of strains) was piM36I (**Table 2**). The rtM184V mutation was present in 70% of strains and was associated with cross-resistance to at least two NRTIs—lamivudine and emtricitabine (**Table 3**). Clinically significant efavirenz resistance was conferred by the rtK103N mutation. ARV resistance was not associated with geographic regions or the CDC pediatric HIV classification. The group of studied children responded satisfactorily to the genotype-guided treatment and intensive family counseling after 52 weeks follow-up.

DISCUSSION

This study is the first to estimate the prevalence of genotypic resistance in treated Saudi children who experienced virologic failure defined as HIV RNA >1000 copies/mL. The ultimate goal of ARV therapy is suppression of HIV replication and reducing morbidity and mortality linked to severe immunodeficiency. During the period from July 2006 to January 2009, about 48% of children living in Saudi Arabia and receiving medical care for HIV infection at King Faisal Specialist Hospital and Research Centre had virologic failure. Among the 22 pretreated children with virologic failure, the prevalence of resistance to any drug was 86.4%, which is higher than previously reported.[3,4,13] Randomized trials and observational studies in children have also described a high prevalence of resistance to any drug, increasing with the number of prior ARV drugs received.[8,14] In

Table 2. Most common resistance patterns in 24 sequences from patients with resistance mutations to protease inhibitor drug susceptibility.

Pattern	No	SQV	ATN	IDV	RTV	NPV	LPV	APV
M36I	17	S	NT	R	R	R	S	NT
L90M	10	R	NT	R	R	R	S	S
L10V	2	R	NT	PR	R	S	S	PR
K20M	3	S	PR	S	R	S	S	PR
G16E	2	S	S	S	S	S	PR	NT
L63T	2	S	S	S	S	S	PR	NT
D30N	9	S	S	S	R	R	S	NT
N88D	8	S	S	S	R	R	S	NT

SQV: saquinavir, ATN: atazanavir, IDV: indinavir, RTV: ritonavir, NPV: nelfinavir, LPV: lopinavir, APV: amprenavir

R: resistant, S: susceptible, PR: possible resistance, NT: not tested

Table 3. The resistance pattern in 14 sequences from patients with resistance mutations in the reverse transcriptase coding region.

Pattern	No	Drug Susceptibility						
		AZT	3TC	D4T	ABC	DDI	FTC	TDF
M184V	10	PR	R	S	S	S	R	S
D67N	3	S	R	PR	R	S	PR	S
K70R	3	PR	S	PR	S	S	S	S
K219E	2	R	S	PR	S	S	S	S
T215Y	3	R	R	R	PR	S	S	S
M41L	2	R	S	R	S	S	S	S

AZT: zidovudine, 3TC: lamivudine, D4T: stavudine, DDI: didanosine, FTC: entricitabine, TDF: tenofovir, ABC: abacavir

R: resistant, S: sensitive, PR: possible resistance.

the United States and western Europe, nearly 80% of HIV-infected adults experiencing virologic failure harbored virus strain resistant to at least one ARV drug.[3,4] Children seem to be more prone to selection for drug-resistant variants for both biologic and behavioral reasons. Plasma viral loads are much higher following perinatal infection and ARV drugs may not fully suppress viral load during the early years of childhood. Furthermore, drug absorption and pharmacokinetics are highly variable and change with age, resulting in suboptimal levels of ARV drug. This is further compounded by difficulties in adherence resulting from unpalatable liquid formulations and the requirement for frequent dosing.[2,8,15,16] The assessment of a child with virologic failure should include evaluation to adherence to therapy, medication intolerance, issues related to pharmacokinetics that could result in low drug levels, and evaluation for ARV drug-resistance testing.[17,18] In our study, 20/22 (91%) viremic patients provided a clear history of noncompliance with HAART because of patient refusal due to the poor taste of the drug. We have observed a high frequency of possible genotypic resistance to PIs (24 mutations). The most common mutations were piM36I and piL90M, found in 70% and 42% of our patients, respectively. These two mutations confer cross-resistance to various PIs. In the present study, we found the best profile for the PIs to be lopinavir (75.5%) with only four possibly resistant isolates as shown in **Table 2**. This observation verifies the important fact that lopinavir has the greatest genetic barrier to resistance. or possible resistance mutations were detected in the RT regions.[19-21]

The most common mutation in RT regions was rtM184V (70%), which was associated with resistance to 3TC and FTC and possible resistance to AZT. This high proportion of patients harboring the M184V mutation could be because 80% of our viremic patients were receiving 3TC at the time of testing. The M184V mutation in the RT gene is associated with resistance to 3TC and inverse susceptibility to others, as has been shown in clinical and in vitro studies.[22-24] RT enzyme possessing the M184V mutation exhibit reduced processability and increased fidelity compared with wild-type enzymes. All patients had genotypic resistance or possible resistance to AZT, D4T and ABC because the pressure of three or more AZT-specific mutations including T214Y is thought to confer resistance to D4T and ABC.[25,26]

We detected the rtK103N mutation in three viremic children who were receiving efavirenz (NRTI). Our data is similar to those described previously by Bacheler et al.[27] The K103N mutation was detected in patients receiving efivarenz and who had a plasma viral load rebound. The K103N is the most common RT gene mutation observed following an NNRT-containing regimen.

Antiretroviral resistance was not associated with geographic region or CDC status. The children had a satisfactory response to genotype-guided treatment. This response was maintained over the follow-up period. Family education concerning adherence was intensive and included training in the administration of the prescribed medication with an emphasis on the importance for adherence to drug regimen.

In conclusion, antiretroviral resistance is common among HIV-infected Saudi children failing HAART. Inadequate adherence is the most common cause of ARV failure in children. The clinician needs to assess the likely contribution of adherence problems to the failure of the drug regimen. M361, M184V and K103N mutations were frequent for the PI, NRTI, and NNRT classes, respectively. These mutations are extremely important as they confer cross-resistance among drugs within the same antiretroviral class. Genotype resistance testing is important to assess reasons for current virologic failure and to identify future selection of active ARV medications. The provided data will help to improve the clinical management of HIV-infected children in Saudi Arabia.

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original article

Quality of life in hemodialysis and peritoneal dialysis patients in Saudi Arabia

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BACKGROUND AND OBJECTIVES: Quality of life (QoL) in end-stage renal disease (ESRD) patients is an important outcome for both physicians and patients in selecting dialysis modality. We conducted a comparison between regular maintenance hemodiaylsis and regular peritoneal dialysis patients in two tertiary referral hospitals in King Saud University in Saudi Arabia. We hypothesize that there might be cultural and socioeconomic factors modifying QoL in dialysis patients.

DESIGN AND SETTING: Cross-sectional study on hemodialysis and peritoneal dialysis patients.

PATIENTS AND METHODS: Two hundred dialysis patients participated in the study, one hundred in each group of dialysis modality, from July 2007 to July 2008. We used a cross-sectional design and collected the date using the Kidney Disease Quality of Life (KDQoL SF) questionnaire.

RESULTS: Patients in both groups had similar sociodemographic characteristics (age, marital status, and education). Mean age (SD) in the hemodialysis group was 47.5 (13.8) years and 51.0 (13.5) years in the peritoneal dialysis group. Males represented 53% and 43%, respectively. Mean duration of dialysis was 77.2 (75.5) months in the hemodialysis group and 34.1 (26.9) months in the peritoneal dialysis group. The mean (SD) score was 49.5 (13.7) in the hemodialysis group and 61.3 (12.4) in the peritoneal dialysis group. QoL mean scores were significantly higher among peritoneal dialysis in all domains and in the total QoL, with the exception of the score of physical QoL, which was higher in the hemodialysis patients, compared to peritoneal dialysis patients, although the difference was not statistically significant. Multiple regression analysis indicated that hemodialysis was a negative predictor of QoL score, compared to peritoneal dialysis. Also, age, male gender, and dialysis duration were negative predictors of QoL score.

CONCLUSION: In the unique culture of Saudi Arabia, peritoneal dialysis patients have better QoL, compared to hemodialysis patients, validating the findings of research reports from other countries.

Health-related quality of life (HRQoL) is an important outcome as well as indicator in end-stage renal disease (ESRD) patients undergoing hemodialysis (HD) or peritoneal dialysis (PD). Hemodialysis is usually performed in a hospital or day care center, three times in a week with each session lasting four hours. However, peritoneal dialysis is usually performed at home which can be done using two systems, continuous ambulatory peritoneal dialysis with four exchanges a day and continuous cyclic peritoneal dialysis with exchanges occuring at night for 8-9 hours using a peritoneal dialysis machine. ESRD imposes substantial effects on the patient's quality of life (QoL) by negatively affecting their social, financial and psychological well-being.[1,2] The disease also affects body image and can have impact on patient's overall QoL and other domains like physical, functional, social and mental status.[3-7] Previous relevant research compared both modalities as well showed that patients undergoing HD or PD treatment were found to experience QoL deficits.[8] A description of a person's QoL should not reflect the opinions of health professionals or family members. QoL measures the individual's subjective perception of his functioning and well-being in his/her day-to-day life.[9] The QoL of HD and PD patients in Saudi Arabia has never been reported.

Both HD and PD patients have diminished QoL scores compared to healthy individuals. QoL declines over time, with the perception of the quality of physical health deterioration than mental health. However, many patients continue to feel hopeless, anxious, and worried about their financial matters, loss of sexual function, family burden, and loss of independence.[10] These studies have demonstrated that the QoL of PD patients was better than that for HD patients.[11] A literature review found no studies on QoL for patients with ESRD and the comparison between the two modalities in Saudi Arabia. Recent statistics of The Saudi Organ Transplant Center (SCOT) in 2008 identified the total number for patients with ESRD as 20 133, with 10 928 (54.3%) on HD and 1112 (5.5%) on PD; 8073 (40.2%) were under follow up after renal transplantation.[12] Moreover, a rapid rise in the incidence of ESRD was also reported in Saudi Arabia, the United States and other countries.[13,16] Our study aimed at comparing the QoL between these two patient groups to validate the findings from other countries in our population considering the unique socioeconomic factors in Saudi Arabia.

Table 1. Sociodemographic characteristics of hemodialysis and peritoneal dialysis patients.

	Dialysis modality		Chi-square test statistic	*P*
	Hemodialysis (n=100)	Peritoneal dialysis (n=100)		
	No. of patients	No. of patients		
Age (years)				
<40	28	19	2.28	.32
40-60	48	53		
60+	24	28		
Range				
Mean (SD)	47.5 (13.8)	51.0 (13.5)	3.4	.07
Gender				
Male	53	43	2	.16
Female	47	57		
Marital status				
Single	40	29	2.68	.1
Married	60	71		
Job status				
Working	37	21	6.22	.01
Unemployed	63	79		
Education				
No formal education	38	34	0.38	.83
Basic/ intermediate	45	47		
High	17	19		
Dependant				
Parent	12	3	19.23	.002
Spouse	37	22		
Sibling	3	4		
Children	29	41		
Self	9	24		
Housekeeper	10	6		

Values are mean (standard deviation) or number (percent) unless otherwise indicated.

PATIENTS AND METHODS

The study included 200 diagnosed cases of ESRD patients more than 18 years old seen between July 2007 and July 2008 at the dialysis clinics of King Khalid University Hospital of King Saud University, and Security Forces Hospital, both in Riyadh, Saudi Arabia. Patients who had cognitive impairment, a focal neurological deficit in the form of paresis/paralysis and psychiatric illness that prevented understanding and responding to the QoL questionnaires were excluded from the study.

A cross-sectional approach was employed to facilitate this QoL study as suggested and used by previous several studies.[17-19] The questionnaire had two sections; a section on basic demographic data, main caregiver and dialysis duration, and a section on the Kidney Disease Quality of Life scale (KDQOL-SF-1.3).[19] The KDQoL scale is disease-targeted and focuses on particular health-related concerns of individuals with kidney disease, patients on dialysis, and the effects of the kidney disease on daily life, the burden of kidney disease, work status, cognitive function, and quality of social interaction, sexual function, social support, dialysis staff encouragement, and patient satisfaction. Its 36 items are categorized into six domains: general health, physical, emotional, social status, illness impact, and financial and medical satisfaction.[20] The scoring of the tool responses was done according to the guidelines of the KDQOL-SF.[19] The questionnaire was translated to Arabic and was reviewed by five experts of different specialities. The author conducted a pilot study using this questionnaire, which was presented as

Table 2. Duration of dialysis in hemodialysis and peritoneal dialysis patients.

Duration of dialysis (months)	Dialysis type		Chi-square test statistic	*P*
	Hemodialysis (n=100)	Peritoneal dialysis (n=100)		
<12	12	15	23.09	<.001
12-60	42	70		
60+	46	15		
Range	2-360	2-144		
Mean (SD)	77.2 (75.5)	34.1 (26.9)	16.11	<.001

Table 3. Quality of life scores of hemodialysis and peritoneal dialysis patients.

	Dialysis type		Mann-Whitney test	*P*
	Hemodialysis (n=100)	Peritoneal (n=100)		
General health				
Mean (SD)	45.8 (17.1)	58 (9.8)	21.85	<.001
Median	39.3	60		
Physical				
Mean (SD)	53.1 (32)	47.7 (23.6)	1.2	.27
Median	47.9	43.4		
Emotional				
Mean (SD)	50.5 (14.8)	61.9 (13.5)	30.85	<.001
Median	47	61.3		
Social				
Mean (SD)	54.9 (18.1)	68.0 (17.5)	20.9	<.001
Median	58.1	70.3		
Illness impact				
Mean(SD)	46.5 (14.2)	63.9 (9.5)	63.32	<.001
Median	43.20	62.65		
Financial and medical satisfaction				
Mean (SD)	45.9 (12.2)	68.4 (13.0)	99.82	<.001
Median	49.30	65.30		
Total				
Mean (SD)	49.5 (13.7)	61.3 (12.4)	36.75	<.001
Median	45.65	62.6		

thesis for a doctorate degree and was published three times in international renowned journals.[20,21] Informed and written consent were secured from patients prior to the interview. Each interview was conducted by the author, thereafter the patient fills up the questionnaire. Forms were collected once patient has completely filled it up. The study protocol was approved by the Ethics Committee- Institutional Review Board of King Saud University, Riyadh, Saudi Arabia and was supported by the Deanship of the Scientific Research College of Medicine King Saud University.

Data entry and statistical analysis were done using the SPSS version 13.0 (IBM Corp, Armonk, New York, United States). Quantitative continuous data were compared using the t test in case of comparisons between two groups. When normal distribution of the data could not be assumed, the non-parametric Mann-Whitney or Kruskal-Wallis tests were used. To identify the independent predictors of patient scores for QoL as dependent factors, and various personal and disease factors as independent factors, multiple linear stepwise backward regression analysis was used, and analysis of variance for the full regression models were done. Statistical significance was considered at $P<.05$.

RESULTS

Among the 200 patients with ESRD who participated in our study, 100 patients were on regular maintenance hemodialysis and 100 patients were on regular peritoneal dialysis (**Table 1**). The highest percentage of patients in both groups of subjects were in the age group of 40 to <60 years, married, unemployed, with basic or intermediate education. The only difference of statistical significance was related to job status (P=.01). More than one third of the hemodialysis patients were working (37%), compared to only about one-fifth (21%) of the peritoneal dialysis group. **Table 1** also shows that the independent patients were 9% of the hemodialysis group, and 24% of the peritoneal dialysis group, and the difference was statistically significant (P=.004). Dependence on the spouse was most common in hemodialysis patients (37%), while dependence on children was most common in peritoneal dialysis patients (41%). The mean (SD) duration of dialysis in the cohort was 77.2 (75.5) months in the hemodialysis group and 34.1 (26.9) months in the peritoneal dialysis group (P<.001) (**Table 2**).

QoL mean scores were higher among peritoneal dialysis in all the domains and in total QoL score, with the exception of the score of physical functioning, which was higher in the hemodialysis patients (53.1 [32]) compared to peritoneal dialysis patients (47.7 [23.6]), although the difference was not statistically significant

(P=0.27) (**Table 3**). Independent predictors of QoL score were age, gender, dialysis duration, and the type of dialysis in a linear regression model (**Table 4**). As evident from the beta coefficients, age and dialysis duration were negative predictors of QoL score. Male gender was a negative predictor compared to female gender. Moreover, HD was a negative predictor of QoL score compared to PD. As the standardized beta-coefficients indicate, the strongest predictors were age and the type of dialysis. The model explains 40% of the variation in QoL score, as the value of r-square indicates. The other sociodemographic and disease characteristics had no independent effect on QoL score.

Table 4. Best fitting linear regression model for the scores of quality of life of hemodialysis and peritoneal dialysis patients.

	Non-standardized coefficients		Standardized coefficients	*t* test	*P*
	Beta	SE			
Constant	56.668	4.474		12.665	<.001
Age	-0.454	0.058	-0.435	7.847	<.001
Gender (reference: male)	4.341	1.586	0.152	2.738	.007
Dialysis duration	-0.041	0.014	-0.174	2.945	.004
Dialysis type (reference: hemodialysis)	11.208	1.708	0.392	6.562	<.001

R-square=0.40; Model ANOVA: F=34.25, P<.001; Variables excluded by model: education, marital status.

DISCUSSION

Patients with ESRD and treated with renal replacement therapy suffer from complications of chronic illness during dialysis. In Saudi Arabia and other countries there are three main medical treatment modalities available: HD, PD and kidney transplantation. Each one has advantages and disadvantages and has different impact on patient QoL. As in other studies, patient characteristics such as age, gender and marital status among Saudi patients treated with HD and PD were statistically similar in effects on QoL.[20]

In our study, QoL mean scores were higher in all domains and total QoL among PD patients compared to HD patients, except the physical QoL score. Our finding is in accordance with several studies that suggested significant advantages for PD in "some" QoL domains.[23] Also other studies showed that patient survival was higher and QoL was better among PD than HD patients.[9] However, patient satisfaction with dialysis care is similar among patients undergoing both modalities of dialysis.[9]

Social functioning and vitality among dialyzed patients decline over time, particularly from 3 to 18 months after onset of treatment.[7] The longer duration of dialysis among our HD patients as compared to our PD patients eventually compromised functioning for their daily activities, thus a more compromised QoL than PD patients.[22] Patients who undergo PD are more at freedom and understandably able to enjoy more valuable time compared to HD patients, since HD patients need longer hours of hospital stay for dialysis. PD patients are also able to continue with their job.[23] Surprisingly though, most of our HD patients were employed and are working. This could be explained by several circumstances that we have to consider such as, the family financial status, number of children, gender, sociocultural factors and employment regulations which give full paid day off for patients in day of dialysis. These reasons may have played a role for a patient to seek employment despite their dependence on the dialysis facility.

The most affected domain of the QoL in our study was the physical health as in previous reports partly due to number of PD exchanges that occur every 6 hours per day in continuous ambulatory peritoneal dialysis (CAPD) patients or because they stay in bed for 8 to 10 hours in automated peritoneal dialysis.[9,23] It is logical that patients who are constrained to a dialysis facility suffer more physical constraints than those who are not dependent on a dialysis facility. Due to this, PD patients have better QoL. Age, male gender, duration of dialysis and HD itself as negative predictors of QoL score could be explained by the higher percentage of male patients in the HD group: only 9% of the HD group was self-dependent compared to 24% in the PD group.

Overall QoL is better among PD than HD patients in all domains except physical domain. PD patients spend more quality time and were more satisfied than HD patients. Moreover, a negative predictors of QoL score were age, male gender, and dialysis duration. Improvement in the quality of life can be acquired in both groups, if exercise programs are properly designed and implemented to meet the demands and needs of the patients.

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original article

Viabahn for femoropopliteal in-stent restenosis

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BACKGROUND AND OBJECTIVES: In-stent restenosis in the femoropopliteal artery is common (20%-40%). Treatment of in-stent restenosis is challenged by poor patency rate. An ePTFE-covered stent-graft (Viabahn) is inert with a very small pore size that does not allow for significant tissue in-growth. Use of a Viabahn stent-graft may improve the patency rate in the treatment of in-stent restenosis.

DESIGN AND SETTING: A retrospective chart review of the use of Viabahn stent grafts implanted in patients with symptomatic femoropopliteal artery in-stent restenosis performed from January 2004 to December 2008.

PATIENTS AND METHODS: We measured the primary patency rate using duplex ultrasound at 1 year and 3 years. We also examined the rate of secondary patency, acute limb ischemia and amputation.

RESULTS: Twenty-seven cases with in-stent restenosis of the femoropopliteal artery treated by Viabahn stent-graft were identified. The average lesion length was 24.5 cm; 52% of the lesions were total occlusion and 37% had critical limb ischemia. The 1- and 3-year primary patency rates were 85.1% and 81.4%, respectively. The secondary patency rate was 96%. All recurrent in-stent restenoses were focal at the proximal and distal edges and none had stent fracture.

CONCLUSION: Our single center experience in a small number of patients showed a favorable patency of ePTFE-covered stent-graft for treatment of patients with in-stent restenosis in the femoropopliteal artery.

In-stent restenosis (ISR) in the femoropopliteal artery (FPA) is common with 20% to 40% rate in the recent trials.[1,2] Restenosis tends to be diffuse and correlate with the length of stented segment, vessel diameter and the presence of stent fracture. Patients with ISR carry the highest risk of recurrent ISR. The results of percutaneous balloon angioplasty (PTA) alone for ISR are dismal.[3] Other modalities include bypass surgery, repeat balloon angioplasty with or without repeat stenting, use of a debulking device such as laser, directional, or orbital atherectomy with or without adjunctive angioplasty, cryoplasty, a drug-eluting balloon, brachytherapy, or use of stent-grafts. Stent-graft may prevent the tissue infiltration and intimal hyperplasia that can lead to ISR. Use of a polyester-covered stent-graft in the FPA was disappointing, with low patency, significant thrombosis rates, and significant inflammatory response.[4-6] The use of ePTFE (expanded polytetrafluorethylene)-covered stent-graft is growing and well documented.

In June 2005, the FDA approved Viabahn (formerly Hemobahn) endoprosthesis (WL Gore and Associates, Flagstaff, Arizona, United States; www.goremedical.com) for superficial femoral artery (SFA) implantation. The stent is a flexible, self-expanding endoluminal graft consisting of an ePTFE lining with an external nitinol support extending along its entire length. There is scarce data evaluating the role of the Viabahn stent-graft for ISR. The Salvage trial (a proSpective, multicenter triAL to eValuate the safety and performance of Spectranetics' laser with adjunct PTA and GORE VIABAHN Endoprosthesis with Heparin Bioactive Surface for the treatment of SFA in-stent restenosis) enrolled 27 patients for SFA ISR, which was terminated prematurely by FDA for further evaluation. We assessed the primary patency rate of Viabahn stent graft when used for bare metal ISR in the FPA.

PATIENTS AND METHODS

The peripheral vascular lab registry database at Saint Elizabeth Medical Center in Boston, Massachusetts, was interrogated to identify patients who had the Viabahn stent graft implantation for ISR in the FPA from January 2004 until December 2008. A retrospective chart review study was then conducted using the electronic medical record database, ultrasound report and images, angiographic reports and images as well as the vascular clinic medical record. The only FDA approved strategy to treat ISR is balloon angioplasty. The use of the Viabahn stent graft is an off-label use for in-stent restenosis. The initial two cases received the first verision of Viabahn and the rest received the newer generation, heparin-coated with contoured edges. Our study protocol was approved by the local review board according to our institutional guidelines.

Patient demographics including age, gender, atherosclerosis risk factors and detailed present history (whether severe claudication or critical limb ischemia) at the time of intervention and details of previous interventions were obtained from the electronic medical record. The baseline ankle-brachial index as well as arterial duplex ultrasonographic data (stenosis or total occlusion) was collected from the ultrasound database in the same institution. Angiographic data were studied from the angiographic films and further procedural details were obtained from notes, including any procedural complications owing to large sheath use. Clinical follow up was traced from the vascular clinic visit medical records. Follow-up arterial duplex ultrasound report and images were studied from a different electronic database.

During the Viabahn stent-graft procedure, all the patients received either heparin (60 U/kg) or bivalirudin. Activated clotting time (ACT) was measured 5 minutes after administration of anticoagulation; the average maximum ACT was 289 seconds. If the ACT was less than 250 seconds, an additional heparin dose (1000-2000 units) was given to target ACT >250 seconds, if the patient was already on heparin. The vessel was prepared before implantation of the Viabahn stent-graft to have a ratio of 1:1. The cutting balloon was used for ostial SFA lesions as well as for suboptimal results (undilatable lesions) after plain PTA to ensure optimal vessel preparation. Three stents were needed in the majority of patients to cover from the angiographically healthy segment to the healthy segment with at least 1 cm of stent overlap. The average Viabahn stent-graft diameter was 5.6 cm and average total length was 26.7 cm. Postdilatation was performed in all patients with extra caution to avoid dilatation outside the Viabahn stent graft margins. The average diameter, length and number of stent-graft implanated in each procedure was 5.6 mm, 274 mm, and 2.6 stent-grafts, respectively (stent-graft number ranged between 1-4 stent-grafts in each procedure). The procedural technical success rate was 100% (defined as <10% residual stenosis by visual estimation). There was only one complication, a distal embolization treated successfully by suction thrombectomy. There was no documented local complications of large sheath use, such as hematoma or pseudoaneurysm; however, arterial punctures were done under fluoroscopic guidance. Adjunctive interventions were performed in 37% of patients to insure at least one vessel runoff, but it was preferable to have two-vessel runoff as well as good inflow. At the end of the Viabahn stent-graft implantation angiogram, 21% of patients had one vessel runoff (53% at baseline), 51% had two vessels run off (21.5% at baseline), and 28% had three-vessel runoff (25% at baseline).

All the patients received clopidogrel (75 mg per day after a loading dose of 600 mg if the patient was not on clopidogrel) in addition to aspirin 81 mg daily. Clopidogrel was used for a minimum duration of 6 months and aspirin indefinitely. We also found that all patients were taking statins, β blockers and angiotensin converting enzyme inhibitors and angiotensin II receptor blockers except one, four and four patients, respectively.

We looked at the primary patency rate using duplex ultrasound at 1 year and 3 years. The definition of significant stenosis (>50%) in our laboratory is when the peak systolic velocity ratio (peak systolic velocity of the arterial segment pre-stenosis to the peak systolic velocity at the stenosis) is more than two. We also looked at the secondary patency rate in a similar manner after target lesion revascularization. We checked for any evidence of stent fracture in patients who had had recurrent ISR. Detailed clinical follow up was recorded including acute limb ischemia, amputation, stroke, myocardial infarction, and surgical revascularization. The ankle-brachial index (ABI) was not done as a surveillance tool, but arterial duplex ultrasound was performed 6 months after the procedure, then annually unless clinically indicated. The surveillance was made to rule out edge restenosis or progression of preexistent inflow or outflow disease. The Rutherford Category was not documented during clinical follow up if the patient remained asymptomatic. In addition, the Rutherford category was also affected by the presence of contralateral disease.

RESULTS

From January 2004 to December 2008, 28 limbs in 26 patients with ISR in the FPA treated by Viabahn stent graft were identified. The demographic data indicated a high-risk population with a mean age of 73 years with more than half diabetic, with chronic kidney disease or coronary artery disease (**Table 1**). The majority

Table 1. Demographic data for 26 patients and 28 limbs.

Mean age (years)	73
Female gender, %	57
Clinical presentation	
Initial bare metal stent procedure	
Intermittent claudication, n (%)	16 (57)
Critical limb ischemia, n (%)	12 (43)
Index Viabahn stent graft procedure	
Intermittent claudication, n (%)	18 (63)
Critical limb ischemia, n (%)	10 (37)
Rutherford Category, n	
3	18
4	7
5	2
6	1
Mean duration from the initial bare metal stent procedure to the index VIABAHN procedure, months (standard deviation)	29.6 (29.5)
Diabetes, n (%)	15 (55)
Hypertension, n (%)	26 (100)
Hyperlipiemia, n (%)	26 (100)
Smoking, n (%)	25 (96)
Coronary artery disease, n (%)	20 (77)
Congestive heart failure, n (%)	6 (22)
Chronic kidney disease, n (%)	14 (53)
Cerebrovascular disease, n (%)	10 (40)
Baseline ankle-brachial index	0.59
Medications, %	
Aspirin	100
Angiotensin converting enzyme Inhibitors	77
Beta blocker	85
Statin	96
Coumadin	0
Cilostazol	8

Table 2. Angiographic data.

Total occlusion, n (%)	
Initial bare metal stent procedure	23 (82)
Index Viabahn procedure	14 (50)
Stenosis, n (%)	
Initial bare metal stent procedure	5 (18)
Index Viabahn procedure	14 (50)
Average bare metal stent length, cm (standard deviation, cm)	18.5 (10.6)
Average bare metal stent diameter, mm (range)	6.4 (5-9)
Average ISR lesion length, cm (range)	24.5 (4-38)
Average vessel diameter, cm (range)	5.52 (5-8)
ISR location, n (%)	
Femoral	6 (21)
Femoropopliteal	18 (64)
Popliteal	2 (7)
Iliac	2 (7)
Previous ISR interventions before Viabahn, n (%)	
Single	4 (14)
Multiple	9 (32)
Baseline number of vessels runoff, n (%)	
One	15 (53)
Two	6 (21)
Three	7 (25)

of patients had severe intermittent claudication (63% Rutherford Category 3), but 37% had critical limb ischemia. Only one patient was taking cilostazol and no patient was taking coumadin. The average baseline and postprocedure ABIs were 0.59 (range 0.25-0.89) and 1.02 (range 0.7-1.4), respectively. In addition, the average lesion length was 24.5 cm and 52% of the lesions were total occlusions (**Table 2**). Not surprisingly, the lesion length had been lengthened from the initial bare metal stent procedure where the total average bare metal stent length was 18.2 cm. Forty-five percent of patients had prior angioplasty to treat ISR with or without laser atherectomy after the initial bare metal stenting and prior to the index Viabahn procedure. All the patients had at least one vessel runoff, and 81% had two or more vessel runoff.

The interventions data are summarized in **Table 3**; laser atherectomy was used in a third of patients followed by balloon angioplasty. **Table 4** shows a subgroup analysis comparing the lesion characteristics pretreated with laser atherectomy versus no laser atherectomy. Most of the laser atherectomy lesions were more likely to be a total occlusion and longer.There were favorable outcomes in the treatment of long ISR of the FPA disease. The one-year and three-year primary patency rates were 85.1% and 81.4%, respectively (**Table 5**). **Figure 1** shows the Kaplan-Meier curve of the re-intervention events after implantation of Viabahn stent-graft for ISR in the FPA. Five patients had recurrent ISR after Viabahn implantation, but focal ISR in both proximal and distal edges and none had stent fracture. Most of the recurrent (4/5) ISR occurred within the first year of follow up. All recurrent ISR patients had stent thromboses due to impaired inflow and outflow of the stent graft. However, only two patients presented with acute limb ischemia and three patients presented as recurrent severe intermittent claudication. Of the acute limb ischemia patients, one prematurely stopped dual antiplatelet therapy and one had prolonged knee-bending posture. Only one patient, who had 2 other recurrences

Table 3. Procedural treatments.

Laser atherectomy, n (%)	10 (35.7)
Predilatation	
Cutting balloon, n (%)	18 (64)
Balloon diameter, average; mm	5.25
Balloon pressure, average; atmospheres	14
Viabahn stent graft	
Diameter, average (range); mm	5.6 (5-8)
Total number implanted, average (range)	2.5 (1-4)
Total length, cm (standard deviation); cm	26.7 (12)
Post dilatation	
Balloon diameter, average; mm	5.5
Balloon pressure, average; atmospheres	15.6
Adjunctive Intervention	
Inflow, n (%)	7 (25)
Iliac PTA and stenting, n	5
Common femoral artery atherectomy,[a] n	2
Outflow and runoff vessels, n (%)	11 (39)
Atherectomy,[b] n	2
PTA, n	2
Stenting,[c] n	7
Profunda femoris artery PTA, n	1
Runoff vessels post-intervention, n (%)	
One	21
Two	51
Three	28

[a] One orbital atherectomy and one rotational atherectomy [b] One laser atherecomy and one orbital atherectomy [c] Two patients received Supera nitinol bare metal stents extended to the below knee popliteal artery and five patients had a drug-eluting stent at one or two of the tibial arteries.

Table 4. Subgroup analysis of laser debulking vs. no laser debulking.

	Laser Debulking (n=10)	No laser Debulking (n=18)
Clinical presentation, n		
Rutherford Category 3	4	14
Rutherford Category 4	3	4
Rutherford Category 5	2	0
Rutherford Category 6	1	0
Total occlusion, n	6	8
Lesion length, average (range), cm	25.5 (10-35)	23.2 (4-38)
Vessel diameter, average (range), cm	5.6 (5-6)	5.6 (5-6)
Average bare metal stent diameter, mm	6.4 (5-9)	
Average ISR lesion length, cm	24.5 (4-38)	
Average vessel diameter, cm	5.52 (5-8)	
Previous ISR interventions before Viabahn, %		
Single	0	4
Multiple	2	7
No. of vessels runoff,[a] n		
One	2	4
Two	6	8
Three	2	6
Viabahn stent graft		
Diameter, average	5.6	5.6
Number, n	2.8	2.5
Cutting balloon use, n	6	12
Adjunctive intervention, n		
Inflow (Iliac/Common femoral)	3[b]	3
Outflow (popliteal/crural vessels)	5	7
Target lesion revascularization, n	1	4
Duration from index Viabahn procedure; days, average (range)	173	576 (241-1164)
Amputation		
Minor, n (time from Viabahn procedure, days)	1 (81)	0
Major, n (time from Viabahn procedure, days)	1 (182)	0

[a] No. of vessels run off before Viabahn stent graft Intervention

[b] Two out of three patients had combined inflow and outflow intervention during the index viabahn procedure

leading to a secondary patency rate of 96%, had a second recurrent Viabahn in-stent restenosis . However, the duration was relatively short (8-18 months) for the rest of the other target lesion revascularization patients. There were two patients with amputations (one minor and one major); both had a patent Viabahn stent graft by ultrasound one month after the amputation. The cause for the major amputation was extensive osteomyelitis for which the patient had a below knee amputation; the patient died a year later due to cancer.

DISCUSSION

To our knowledge this is the first reported study of the 3-year patency of Viabahn stent-graft for treatment of ISR in FPA disease. We found very favorable outcomes in the treatment of complex long FPA ISR using Viabahn stent-graft with three-year primary patency rates of 81%. Our data support the use of Viabahn stent-graft for complex long FPA ISR in a carefully selected patient population by the operator. A suggested guideline or opinion for use of Viabahn is summarized in **Table 6**. This complete guideline is formulated after the completion of the study based on the operator's experience. **Figure 2** shows one example of 54-year-old male known to have coronary artery disease and lifestyle disabling intermittent claudication (Rutherford category 3). He had had multiple interventions due to in-stent restenoses and finally became asymptomatic

Table 5. Clinical outcomes in 28 limbs of 26 patients.

Primary patency rate	
One year, %	85.1
Three year, %	81.4
Post-Procedure ABI, average	1.01
Amputation	
Major, n	1
Minor, n	1
Long term follow-up	
Stroke, n	1
Myocardial infarction, n	1
Stent fracture rate, n	0

ABI: Ankle Brachial Index

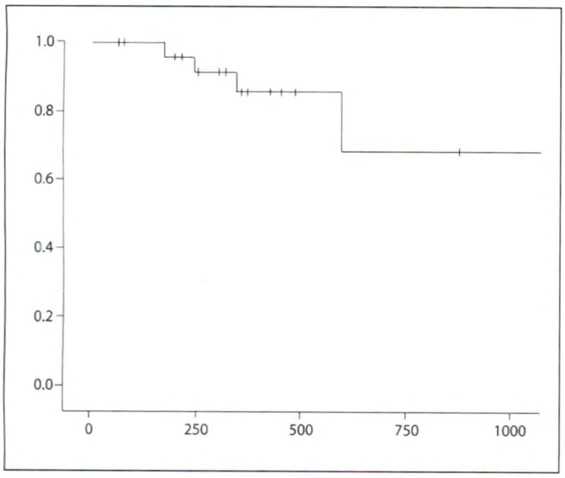


Figure 1. Kaplan-Meier curve of re-intervention events after implantation of Viabahn stent.

since the implantation of Vibahn stent grafts 4 years previously.

Three out of the five recurrent ISR cases presented as severe intermittent claudication, Rutherford category 3. Despite two patients who presented with acute limb ischemia (7%), Rutherford category 4, they were potentially preventable by means of dual antiplatelet therapy, especially in the first six months postimplantation as well as avoidance of prolonged knee bending postures. The rate of stent graft endothelialization was studied by Marin et al[7,8] who showed that endothelialization can cover up to 8 cm of the stent-graft at 5 months post-implantation. Therefore, we generally recommend continuing dual antiplatelet therapy beyond six months if there is no high bleeding risk or cost concerns because recurrent ISR occur at the stent's edges. It is also well documented in bypass graft reports that bending of the affected limb will kink the endovascular graft leading to cessation of the blood flow leading to graft thrombosis.

Table 6. Suggested guidelines for use of Viabahn.

Preimplantation

- Good Inflow
- Acceptable outflow with at least one patent vessel runoff
- Vessel diameter at least 4.8 mm
- Avoid in heavily calcified arteries
- Prepare the lesion to have artery: stent graft ratio of 1:1
- No planned surgery for the next 6 months
- Caution in patients at high risk of bleeding

Implantation

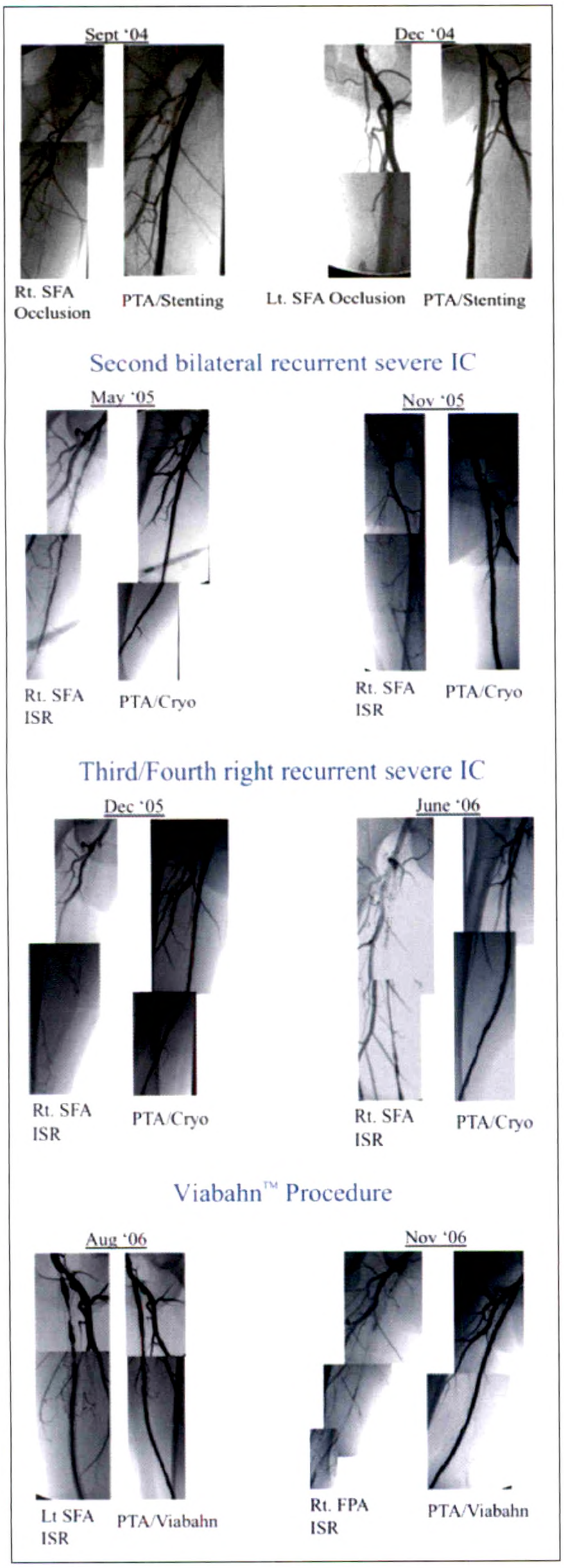
- Avoid stent graft oversizing to prevent enfolding which can be a nidus for stent thrombosis
- Optimal and cautious post dilatation to avoid dilating stent edges which can be a nidus for edge in-stent restenosis
- Cover the lesion completely from healthy angiographic segment to another healthy angiographic segment
- At least 1 cm of stent graft overlap if more than one Viabahn stent graft were needed
- Cautious implantation in ostial SFA to avoid jailing deep profunda artery

Postimplantation

- Dual antiplatelet therapy for at least 6 month followed by lifelong aspirin
- Avoid prolonged knee bending positions
- Ultrasound surveillance particularly in the first year postimplantation

Treatment of ISR in the lower extremities is one of the most challenging pathologies. There are more than 150 000 FPA stent procedures per year in United States.[9] In the most recent trials, the rate of ISR is as common as 40%. Thus, the burden of FPA ISR may reach up to 60 000 cases per year in this country. The only FDA-approved treatment of ISR is PTA. However, Rocha-Singh et al showed in a survey of randomized control trials that the PTA control–arm data have estimated a 12-month primary patency (by duplex ultrasound) of only 33% for lesions 4 to 15 cm long.[10] Not surprisingly, the patency of PTA for ISR was even worse. Dick P et al[3] randomized 40 patients to conventional balloon angioplasty versus cutting balloon for ISR with a mean lesion length of 8 cm. They found that primary patency rates were only 27% to 35% at 6 months. Use of atherectomy devices was also disappointing. Treatment using excisional atherectomy on 43 limbs with in-stent restenoses and a mean lesion length of 13.1 cm showed a one-year primary patency rate of 54%.[11] Anecdotally, repeat stenting will invariably increase the risk of ISR as well as risk of stent fracture since the lesion will be longer and less flexible. Scheinert et al[12] showed the risk of stent fracture in non ISR lesions is as high as 52% if the lesion length was more than 16 cm and the stent fracture would lower the patency rate by half compared to a non-fractured stent

Figure 2. Case illustration.



particularly in the first two years postimplantation as seen in a different study.[13]

While there were multiple small studies for Viabahn stent-graft to treat de novo FPA lesions, there are minimal data using Viabahn stent-graft for ISR.[14] Recurrent ISR of Viabahn stent graft is almost always at the edges and subsequently its patency is independent to the lesion length but dependent on the Viabahn stent diameter.[15] **Table 7** summarizes the published Viabahn patency data with relation to the lesion length. Viabahn stent graft is more flexible (but not kink-free stent) than a bare metal stent, which would reduce the risk of stent fracture and its consequences. In this study, no stent fracture was noted in patients who came for recurrent intervention or as a control when a procedure elsewhere was performed; only 10 patients were specifically examined for fracture. The Viabahn stent-graft has a low tendency to jump during delivery. This makes it reliable for implantation, though carefully, up to the ostium of the SFA. Two orthogonal views are needed before implantation to insure coverage of the ostium of the SFA and so as to not inadvertently cover the ostium of the deep profunda femoris artery. According to the operator experience, the Viabahn stent-graft should be avoided in heavily calcified lesions or if the vessel diameter is less than 5 mm to avoid enfolding of the Viabahn stent graft. Enfolding of stent-graft may function like a nidus for stent thrombosis. Like in prosthetic bypass graft surgery, an endovascular stent-graft also requires adequate inflow and outflow as well as avoidance of prolonged knee bending postures to prevent kinking of the stent graft which would lead to cessation of the blood flow and stent thrombosis.

Ansel G et al[15] showed a similar favorable outcome in ten patients with diffuse nitinol stent restenosis in the femoropopliteal artery treated with Viabahn stent-graft. The primary, assisted primary and secondary patency rates were 70%, 80%, and 90%, respectively after at least one year of follow up. The Salvage trial, which is the only randomized control trial to date using the Viabahn stent graft for ISR in the SFA, was suspended after the enrollment of 27 patients due to FDA concerns about the interaction between laser therapy and the nitinol stent. The results of the enrolled 27 patients are still pending.

The limitations of Viabahn stent graft include coverage of collaterals, which would put the patient at risk of acute limb ischemia if the stent graft is thrombosed. However, in our study the two patients who presented with acute limb ischemia may have had explainable causes (one prematurely stopped dual antiplatelet therapy and one had prolonged knee bending posture). It is

Table 7. Viabahn Stent Graft for de novo femoropopliteal disease.

Study	No. of limbs	Lesion length, cm	1-yr patency rate, %	Comments
Farraj et al[13]	32	15.4	94	Chronic total occlusion study
Saxon et al[14]	87	14.2	76	4-yr patency, 55%
Kedora et al[15]	50	25.6	73.5	Similar to prosthetic bypass surgery
Fischer et al[16]	48	10.7	80	6-yr patency, 57%
Hartung et al[17]	34	10.8	85	2-yr patency, 85%, TASC D excluded
Bleyn et al[18]	67	14.3	82	5-yr patency, 47%
Jahnke et al[19]	52	8.5	74	2-yr patency, 62%
Lammer et al[20]	80	13.8	78.7	No thienopyridine, high thrombosis rate

TASC: TransAtlantic InterSociety Consensus Classification, D indicating chronic total occlusion of the popliteal artery and proximal trifurcation vessels.

unwise to intentionally keep gaps in between multiple stent grafts to preserve collaterals since it would be a source for restenosis. The concern of using catheter-directed thrombolysis in all the patients in this study with recurrent ISR of Viabahn stent-graft is well taken, but may be closer follow up (particularly in the first year postprocedure) can select those patients with edge ISR for further short touch angioplasty, preferably using a drug-eluting balloon. The data for drug-eluting balloons in peripheral vessel showed favorable late lumen loss.[16,17] The Viabahn stent graft is easily detected by duplex ultrasound making the diagnosis of edge restenosis easy and accurate. In addition, it is crucial to assess for any inflow and particularly outflow disease during ultrasound follow up which also can jeopardize the patency of Viabahn stent-graft without having edge ISR, eg, popliteal artery stenosis may lead to stagnation of blood flow in the Viabahn endoprosthesis, which will lead to stent thrombosis despite the absence of edge ISR. The secondary patency rate in our study is limited by the paucity of days of follow up. It ranged between 3 months to 2 years for the five patients who had re-interventions after Viabahn stent-graft implantation.

In summary, our experience in a small number of patients showed a very favorable result with an ePTFE covered stent-graft (Viabahn) for patients with in-stent restenosis in the femoropopliteal artery with a 3-year primary patency rate of 81%.

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Characteristics of Saudi patients with congestive heart failure and adherence to management guidelines in a tertiary hospital in Riyadh

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BACKGROUND AND OBJECTIVES: There is limited data available on the characteristics of local Saudi patients diagnosed with congestive heart failure (CHF) and on their adherence to guidelines for managing the disease. This study aimed to fill this gap.

DESIGN AND SETTING: Retrospective study of patients treated at King Abdulaziz Medical City from 2002-2008.

SUBJECTS AND METHODS: The records were reviewed of subjects admitted secondary to heart failure (defined as systolic heart failure [ejection fraction <55%] and/or heart failure with preserved ejection fraction diagnosed either clinically and/or by echocardiogram and/or cardiac catheterization) or who visited the outpatient department for the same complaint.

RESULTS: Of 392 CHF cases, the mean age was 67.8 (12.8) years and the majority were males (53.1%). Hypertension was the predominant comorbid illness, accounting for 84.9% of cases, followed by diabetes mellitus type 2 and hyperlipidemia. Almost three-fourths (73.7%) of the subjects had mild to severe left ventricular dysfunction, with 68.5% of the cases having right ischemic cardiomyopathy. Spironolactone, exercise and vaccination were the the least least adhered to recommendations (30.0%, 20.5% and 15.2%, respectively).

CONCLUSIONS: The study highlights the need for proper education of patients and caregivers to increase compliance to medications. Physicians are also encouraged to undergo continuing medical education and training courses to properly implement current recommendations in the management of heart failure. Further studies are needed on a larger scale in order to formulate an effective management scheme that will address the current challenges faced by both clinicians and CHF patients.

One of the mostly affected human organs in terms of rapid industrialization and urbanization is the heart.[1] While the industrialized Western and European nations' prevalence of heart diseases begin to taper off,[2] the prevalence in developing nations is strikingly increasing, accounting for more than 80% of the cause of death in these nations.[3] These vascular diseases are widely known not only as public health threats and economic burdens, but more so because these diseases increase morbidity and mortality, not to mention the over-all quality of life of the individual. To further complicate management of these diseases are the modifiable and non-modifiable cardiovascular risk factors (ie, age, family history, obesity, dyslipidemia, smoking). The presence of one risk factor alone can cause the disease, but the presence of other risk factors combined increases the likelihood of harboring these diseases. In Saudi Arabia alone, the recent epidemiologic study done by Al-Daghri and colleagues highlighted the worsening prevalence of diabetes mellitus, hypertension and coronary artery disease in the capital Riyadh as compared only to the previous decade.[4] Furthermore, the prevalence of metabolic syndrome (the clustering of cardiometabolic risk factors) is still alarmingly high in the country in both children[5] and adults.[6]

Among the roster of chronic non-communicable diseases involving the heart is congestive heart failure (CHF). CHF, or heart failure, in general, is the weakening of the heart's ability to effectively pump blood. Recent epidemiologic studies observed a declining trend in heart failure hospitalizations in US,[7] but not in European nations such as England and Wales,[8] indicating discrepancies in trends and management even in developed nations. While epidemiologic data in Saudi Arabia and the Middle East and North Africa are limited, the recent study of Magaña-Serrano and colleagues observed a lower incidence of heart failure with preserved systolic function in the Middle East as compared to Latin America and North Africa, where the prevalence of coronary artery disease and hypertension was observed to be greater.[9] Furthermore, Arab patients presenting with acute coronary syndrome (ACS) with prior coronary artery bypass graft (CABG) were observed to have more severe left ventricular dysfunction but with a less prominent surge of cardiac biomarkers as compared to patients from other regions.[10] In Saudi Arabia, hypertension is present in more than 80% of patients with heart failure, making it the single strongest predictor of CHF.[11] This was later confirmed from a recent study by Assiri, indicating that both hypertension and ischemic heart disease are the major causes of heart failure among elderly Saudis.[12] Despite these observations, little has been mentioned as to the adherence of Saudi CHF patients to current management guidelines. This single-center study, done at a major tertiary hospital in Riyadh aimed to fill this gap.

SUBJECTS AND METHODS

In this retrospective study done at King Abdulaziz Medical City, Riyadh, Saudi Arabia, we reviewed and screened the medical records of 500 patients admitted secondary to heart failure (defined as systolic heart failure [ejection fraction <55%] and/or heart failure with preserved ejection fraction diagnosed either clinically and/or by echocardiogram and/or cardiac catheterization) or who visited the outpatient department for the same complaint between the years 2002-2008. Cases were excluded if the heart failure was congenital in origin, end-stage renal disease (ESRD) was present, and if the patient was older than 90 years of age. From the roster of cases, a total of 392 cases met the criterion for this study. Information gathered included demographics, medical history, including functional classification of heart failure based on the recommendations of the New York Heart Association (NYHA)[12] (**Table 1**)

Table 1. The New York Heart Association Classification System.[12]

Class	NYHA Functional Classification
I	Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain
III	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea or anginal pain
IV	Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased

Table 2. Patient characteristics (n=392).

Males	208 (53.1)
Age (years)	67.8 (12.8)
NYHA Class (mean, SD)	2.7 (0.9)
NYHA 1	53 (13.6)
NYHA 2	67 (17.1)
NYHA 3	203 (51.9)
NYHA 4	68 (17.4)
Mortality	205 (52.3)
Hypertension	333 (84.9)
Smokers	60 (15.3)
Hyperlipidemia	233 (59.4)
Diabetes mellitus type 2	242 (61.7)
Left ventricular dysfunction (EF <55%)	289 (73.7)
Normal ejection fraction (EF ≥55%)	101 (25.8)
Valvular disease	45 (11.5)
Ischemic cardiomyopathy	268 (68.5)
Chronic atrial fibrillation	103 (26.3)
PTCA/CABG	91 (23.2)
Stroke/transient ischemic attack	89 (22.7)

Data presented as N (%) or mean (SD). PTCA: percutaneous transluminal coronary angioplasty, CABG: coronary artery bypass graft

Table 3. Medications taken by study subjects.

Angiotensin-converting enzyme inhibitors	175 (45.1)
Angiotensin receptor blocker	135 (34.8)
β-blockers	269 (69.3)
Diuretics	298 (76.8)
Spironolactone	88 (22.7)
Statins	273 (70.7)
Nitrates	52 (17.7)
Anti-arrhythmic	22 (5.7)
Digitalis	55 (14.2)
Aspirin	241 (62.3)
Warfarin	70 (18.1)
Plavix	85 (22.0)
CRT, ICD, Combined	35 (9.0)

Data are n (%). CRT: cardiac resynchronization therapy, ICD: intracardiac defribrillator.

Table 4. Metabolic characteristics of subjects.

Hemoglobin (g%)	117.3 (23.0)
Creatinine (mg/dL)	150.9 (126.2)
Blood urea nitrogen (mmol/L)	13.3 (9.4)
Glucose (mmol/L)	10.0 (5.5)
Total cholesterol (mmol/L)	3.6 (1.2)
HDL-cholesterol (mmol/L)	1.0 (0.3)
LDL-cholesterol (mmol/L)	2.3 (0.9)
Triglycerides (mmol/L)	1.6 (0.9)
Albumin (g/L)	34.8 (7.0)
Potassium (mEq/L)	4.4 (0.7)
Sodium (mEq/L)	137.4 (32.2)

Data are mean (SD).

and medications taken. Laboratory results obtained during admission/evaluation were also obtained and included fasting plasma glucose, lipid and renal profiles as well as electrolytes. Raw data were encoded in a Microsoft Excel spreadsheet. Data was analyzed using SPSS, (IBM Corp, Armonk, New York, United States). Frequencies were presented as percentage (%) and continuous variables were presented as mean (standard deviation). The chi-square test was used for the comparison of frequencies. Significance was set at $P<.05$.

RESULTS

The majority of the subjects were elderly and more than half were male (**Table 2**). More than half (51.9%) had marked limitation in their physical activity (NYHA Class III), and 52.3% of the cases eventually died. Hypertension was the predominant comorbid illness, accounting for 84.9% of cases, followed by diabetes mellitus type 2 and hyperlipidemia. Consequently, almost three-fourths (73.7%) of the subjects suffered from mild-to-severe left ventricular dysfunction, with 68.5% of the cases having ischemic cardiomyopathy (**Table 2**). The majority of the subjects were taking diuretics (76.8%), statins (70.7%), β-blockers (69.3%) and aspirin (62.3%) (**Table 3**). **Table 4** shows the metabolic profile of the subjects. **Table 5** compares the subjects according to type of ventricular dysfunction. Those with reduced ejection fraction (EF < 55) had a higher incidence of coronary artery disease, but more were taking angiotensin-converting enzyme inhibitors, β-blockers, spironolactone and digitalis ($P<.01$) as compared to those with preserved EF (EF ≥55). The rest of the parameters were comparable. **Figure 1** shows the number of percentage of subjects complying with the recommendations set by the American College of Cardiology and American Heart Association. Exercise and vaccination were the least complied with recommendations (20.5% and 15.2%, respectively), with barely one-fifth of the subjects adherent.

DISCUSSION

The major findings of this study highlight similarities done previously in the same ethnic group in terms of dominating risk factors (hypertension and diabetes mellitus) as well as the presentation of subjects (ie. elderly, male gender).[13,14] What the present study adds to the literature is adherence to current recommendations. In the present study, the majority of subjects were compliant in terms of salt and fluid restriction, as well as intake of vasodilators. What was apparent was the decreased compliance to spironolactone, as well as exercise and vaccination. Current recommendations in both European and American cardiology societies are in agreement in terms of management of heart failure,[15] and these consensuses are applied universally, including the tertiary hospital where this study was conducted. The difference therefore lies in the adherence of patients involved, as well as the dominant risk factors, which vary regionally. Both diabetes mellitus and hypertension are common in Saudi Arabia,[4] and in the Middle East in general.[16] Furthermore, dyslipidemia is extremely common in both adults and children,[5,6] which means that CHF risk factors in the country start to

Table 5. Comparison between subjects with heart failure and reduced ejection fraction versus heart failure and preserved ejection fraction.

	EF <55%	EF ≥55%	*P*
Hypertension	245	88	.51
Diabetes mellitus	173	69	.11
Coronary artery disease	230	59	< .001
Atrial fibrillation	67	24	.54
Stroke/transient ischemic attack	64	25	.38
Dyslipidemia	175	88	.26
Mortality	143	44	.14
Angiotensin-converting enzyme inhibitors	147	28	< .001
β-blockers	223	46	< .001
Digitalis	240	94	.001
Spironoloctone	79	9	< .001
Diuretics	219	79	.40
Angiotensin receptor blocker	102	33	.35

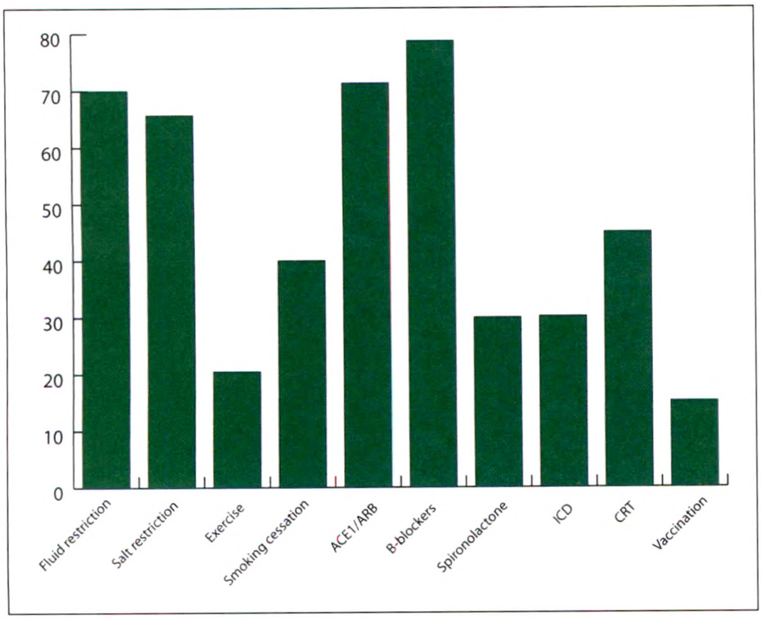

Figure 1. Percentage (%) Adherence to ACC/AHA guidelines in managing CHF patients with reduced EF.

manifest as early as childhood. Subjects included in this study also had a sedentary lifestyle, which is also very common in Saudi Arabia,[17] and probably explains the lack of adherence to exercise. As to less compliance to medications, perhaps one of the issues that predispose heart failure patients not to adhere to current recommendations is polypharmacy. Patients harboring more than one disease are subject to multiple management schemes, making them prone to polypharmacy while at the same time increasing their risk of nonadherence. Regardless, polypharmacy by itself is rampant in different primary care centers in the country.[18,19] Lastly, physicians themselves need to be educated about the standard recommendations for management of CHF. In one study done in Aseer, it was observed that only one-fifth of the physicians prescribed a diuretic as the preferred initial anti-hypertensive medication.[20] This could have huge implications in the overall implementation of standard treatment.

Patients and their respective care takers should be educated properly about the disease they harbor to increase compliance to medications. Physicians are also encouraged to undergo continuing medical education and training courses to properly implement current recommendations in the management of heart failure. Further studies are needed on a larger scale to formulate an effective management scheme that will address the current challenges faced by both clinicians and patients harboring heart failure.

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Ovarian volume assessment in relation to histologic findings and sex hormone levels in women with postmenopausal bleeding and thickened endometrium

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BACKGROUND AND OBJECTIVES: In postmenopausal women, ovarian stromal hyperplasia and endometrial cancer are often identified concurrently. The aim of the present study was to verify the association of ovarian volume with histologic findings and sex hormones levels in women with postmenopausal bleeding and thickened endometrium.

DESIGN AND SETTING: Prospective observational study conducted in a teaching hospital between March 2008 and February 2010

PATIENTS AND METHODS: Ninety women with postmenopausal bleeding and thickened endometrium ($\geq$5 mm) were enrolled. They underwent vaginal sonography for ovarian volume measurement. Blood samples were collected for sex steroid hormones assay. In addition, endometrial sampling was done for definitive histologic diagnosis.

RESULTS: According to histologic results, 18 cases (20%) had endometrial adenocarcinoma, 24 cases (26.7%) had endometrial hyperplasia with or without atypia and 48 cases (53.3%) had benign histologic findings. Large ovaries were significantly associated with higher body mass index (BMI$\geq$30) (P=.002) and endometrial adenocarcinoma (P<.001). After adjustment for age and BMI, increased ovarian volume in adenocarcinoma was associated with high serum level of estradiol (P<.001), serum total testosterone (P=.04) and serum free testosterone (P<.01) compared with other histologic findings.

CONCLUSIONS: Large ovaries among women with postmenopausal bleeding and thick endometrium were associated with elevated serum sex steroid hormones and represent a marker of risk for endometrial adenocarcinoma.

Postmenopausal endometrial thickening is a nonspecific finding that may be caused by a variety of conditions, such as carcinoma, polyps, hyperplasia, endometritis, or cystic atrophy. However, postmenopausal bleeding is usually the first symptom; only 10% to 15% of women with postmenopausal bleeding will actually have endometrial cancer and the risk becomes low when double-layer endometrial thickness is <5 mm.[1,2]

Postmenopausal women with high levels of circulating estrogens or androgens are at increased risk for developing breast and endometrial cancer.[3, 4] Recognition that aromatization of androgens to estrogens in peripheral adipose tissue represents the main source of circulating estrogens among postmenopausal women, thereby linking obesity, elevated circulating estrogen levels, and increased endometrial carcinoma risk.[5]

Postmenopausal ovaries consist largely of stroma, which includes hormone synthesizing cells. Larger ovaries were more likely to contain luteinized cells and hilar cells, overall suggesting a link between size and potential for hormone synthesis.[6] Ovarian stromal hyperplasia and endometrial cancer are often identified concurrently, suggesting that ovarian morphology may represent a marker of cancer risk among older women.[7] This association may reflect increased production of androgen, the main hormone product of the postmenopausal ovary. Our aim was to analyze the relationships between ovarian volume and endometrial histologic findings, serum sex hormones levels in women with postmenopausal bleeding and thickened endometrium.

PATIENTS AND METHODS

This study was carried out between March 2008 and February 2010 in the Department of Obstetrics and Gynecology, Ohud hospital, one of the Taibah university teaching hospitals, Al-Madinah Al-Munawarah province, Saudi Arabia. A series of women with one or more episodes of postmenopausal vaginal bleeding participated in this study. The inclusion criteria were (1) postmenopausal bleeding, defined as vaginal bleeding after 12 months of menopause in women older than 45 years and (2) double layer endometrial thickness of ≥ 5 mm as measured by baseline transvaginal sonography. Exclusion criteria were (1) endometrial thickness <5 mm, (2) use of any kind of hormone replacement therapy in the 6 months prior to the study and (3) inability to visualize either ovary by transvaginal sonography.

Diagnostic work-up included a complete medical history, physical examination and transvaginal ultrasound examination (TVU) (Toshiba SSA 270A/HG Tokyo Japan, vaginal probe 7.5 MHz). Maximal endometrial thickness (double layer) was measured in the longitudinal plane. Written informed consent was obtained from all patients. The study protocol was approved by the Medical and Health Sciences Research Committee Involving Human Subjects of Ohud Hospital, which conforms to the provisions of the Declaration of Helsinki.

To estimate the ovarian volume, the following ovarian dimensions were measured: maximum longitudinal (D1), anteroposterior (D2), and transversal (D3) diameters. Ovarian volume was then calculated as: $D1 \times D2 \times D3 \times 0.523$.[8] Mean ovarian volume was calculated when both right and left ovaries could be measured by ultrasound. When only one ovary could be measured by ultrasound, its measurement was considered to be the patient's ovarian volume.[9] All women had donated a blood sample at time of ultrasound evaluation that was assayed for estradiol, estrone, sex hormone-binding globulin (SHBG), androstenedione, total testosterone and free testosterone using ELISA (GenWay Biotech, Inc, San Diego, California, USA). In addition, the participants underwent endometrial sampling within a few days by hysteroscopy or dilatation and curettage. A definitive histologic diagnosis was obtained in all cases.

Body mass index (BMI) was calculated by dividing weight in kilograms by height squared (m^2), and categorized as <25.0, 25.0–29.9, and ≥ 30.0 kg/m^2.[10] Data related to age at menopause and parity (0 vs. 1+) based on the number of vaginal deliveries and/or cesarean deliveries was obtained through nurse interviews.

The statistical analysis was done using SPSS Version 13 for Windows (IBM Corp, Armonk, New York, United States). Values are given as mean (standard deviation) or number (percentage). The paired *t* test was used for quantitative variables and the χ^2 or Fisher exact test for qualitative variables. Ovarian volume for each demographic character is presented as age-adjusted geometric means. Levels of SHBG and sex steroids were log transformed to normalize their distribution. We assessed the geometric mean ovarian volume in each histologic group to log-transformed hormones and SHBG levels adjusted for categories of age (≤ 50, 51-57, 58-64, ≥ 70 years) and BMI (<25.0, 25.0-29.9, ≥ 30.0 kg/m^2)[11] and compared using the Fisher exact test, and then repeated the analysis focused on obesity (BMI ≥ 30.0). $P \leq .05$ was considered significant and the 95% confidence interval is reported.

RESULTS

During the study period, 103 women with postmenopausal bleeding and a thickened endometrium (≥ 5 mm) were evaluated. Thirteen patients were excluded. The following findings led to exclusion: no definitive histopathologic diagnosis (4 patients), ovarian cyst (3 patients) and inability to measure either ovary (6 patients). Ninety women were included in the study. Only one ovary could be measured by TVU in 8 women. Five women underwent hysterectomy due to recurrent postmenopausal bleeding, but they were included in our study after they had a definitive histologic diagno-

Table 1. Epidemiologic and medical characteristics in women with postmenopausal bleeding according to histologic results of thickened endometrium.[a]

Characteristics	Benign[b] n=48	Hyperplasia n=24	Adenocarcinoma n=18	P
Age (y)	58.8 (4.2)	59.3 (3.6)	61.2 (4.0)	.081
Parity (%)				
Nulliparous	18.50	14.32	20.75	.17
Parous	81.45	85.70	79.25	
BMI (kg/m²)	24.3 (2.3)	25.6 (4.2)	28.7 (7.4)	<.001
Age at menopause (y)	46.2 (1.3)	48.2 (4.2)	54.1 (2.1)	.033
Diabetes (%)	14.8	16.2	18.75	.7
Hypertension (%)	25.9	28.5	31.2	.3

[a] Values are given as mean (SD) or number (percentage).

[b] Benign endometrial histology included (endometritis, submucous myoma and endometrial polyp)

sis. According to histologic results, 18 cases (20%) had endometrial adenocarcinoma, 24 cases (26.7%) had endometrial hyperplasia with or without atypia and 53.3% had benign histologic findings as endometritis (7 cases), submucous myoma (9 cases) and endometrial polyp (32 cases).

Epidemiologic and medical characteristics of the sample are shown in **Table 1**. Adenocarcinoma showed a significant higher age at menopause and higher BMI ($P=.033$), ($P<.001$), respectively. **Table 2** showed that the mean ovarian volume decreased from 2.03 cm^3 among women aged 50 years or less to 1.89 cm^3 among women aged 70 years or older, but there was no significant difference ($P=.071$). Increased ovarian volume was associated significantly with higher BMI ≥30 ($P=.002$). Mean ovarian volume, adjusted for age and BMI, was significantly related to endometrial adenocarcinoma ($P<.001$).

Table 2. Mean ovarian volume (cm) in relation to age, parity, BMI (kg/m^2) and histologic results of thickened endometrium in women with postmenopausal bleeding.

Variable	N	MOV (cm^3) (95% CI)	P
Age (y)			
≤50	13	2.03 (1.91-2.14)	.071
51-57	22	1.97 (1.86-2.05)	
58-64	38	1.96 (1.84-1.99)	
≥70	17	1.89 (1.80-1.94)	
Parity			
Nulliparous	18	1.81 (1.77-1.89)	.18
Parous	72	1.83 (1.75-1.90)	
BMI (kg/m^2)			
<25	18	1.73 (1.69-1.87)	.002
25-29.9	30	1.85 (1.80-1.96)	
≥30	42	2.08 (1.94-2.12)	
Histologic results			
Benign histology	48	1.80 (1.74-1.84)	<.001
Hyperplasia	24	1.91 (1.87-1.98)	
Adenocarcinoma	18	2.10 (1.99-2.13)	

MOV: mean ovarian volume, Ovarian volumes are presented as age-adjusted geometric means

The women who presented with endometrial adenocarcinoma and increased ovarian volume, after adjustment for age and BMI, had significantly higher serum levels of estradiol ($P<.001$), total testosterone ($P=.04$) and free testosterone ($P<.01$) compared with the other two histologic findings (**Table 3**).

DISCUSSION

The main finding in this study was that ovarian volume measurement associated with serum sex steroids are good diagnostic tools in predicting endometrial carcinoma in patients with postmenopausal bleeding and a thick endometrium. Previous analyses had considered large postmenopausal ovaries as a marker of risk for endometrial carcinoma.[7,12] Ovarian enlargement in women who present with postmenopausal bleeding and a thick endometrium may represent a marker of hormonal imbalance—mostly higher androgen levels (current, past or at both times), which indicates a greater availability of substrate for estrogen synthesis in peripheral adipose tissue and is a factor that could increase the risk for endometrial cancer.[13,14]

Transvaginal sonography is currently considered as a first step to rule out endometrial carcinoma in women with postmenopausal bleeding when endometrial thickness is <5 mm.[1,15] However, a thick endometrium is a nonspecific finding; most current protocols include use of hysteroscopy or endometrial office biopsy for histologic diagnosis.[16,17] For purposes of this study, we included only women with a thick endometrium (≥5 mm) because they are at a high risk for endometrial cancer.[18] Due to this selection criteria and the small sample size, our incidence for endometrial adenocarcinoma was higher (20%). Ovarian assessment in this study was based on transvaginal ultrasound, precluding assessment of characteristics such as ovarian stromal hyper-

Table 3. Geometric mean (95% confidence interval) of serum factors by ovarian volumes among different histologic groups.

Steroid hormone	Benign MOV (1.80cm^3)	Hyperplasia MOV (1.91cm^3)	Adenocarcinoma MOV (2.10 cm^3)	P
Estradiol (pg/mL)	5.1 (2.6-7.3)	6.3 (3.1-8.1)	10.8 (8.2-13.4)	<.001
Estrone (pg/mL)	32 (27-39)	33 (26-42)	35 (29-45)	.25
SHBG (nmol/L)	26.8 (22.1-36.2)	25.6 (23.2-38.4)	26.1 (20.1-35.2)	.70
Androstenedione (ng/mL)	52 (40-61)	54 (42-65)	53 (42-60)	.31
Total testosterone (ng/mL)	0.43 (0.20-0.51)	0.52 (0.32-0.62)	0.61 (0.48-0.59)	.04
Free Testosterone (ng/mL)	2.1 (1.6-2.8)	3.2 (2.4-3.7)	6.4 (3.8-8.7)	<.01

SHBG: sex hormone binding globulin, MOV: mean ovarian volume, Geometric means of serum factors Levels are adjusted for age and body mass index plasia. However, in noncystic postmenopausal ovaries, stroma accounts for great majority of its volume.[19]

The present study showed that obesity was associated with increased endometrial cancer risk in postmenopausal women as established previously.[20] The prevailing hypothesis is that this association can be explained by increases in the amount of bioavailable estrogens in the circulation and endometrial tissue via peripheral conversion of adrenal and ovarian androgens, mostly within adipose tissue.[21]

In this analysis, the mean ovarian volume declined from 2.03 cm^3 among women aged 50 years or less and to 1.89 cm^3 among women aged 70 years or more, but the magnitude of the change was small and not statistically significant. Previous studies on asymptomatic, bleeding-free postmenopausal women reported inverse associations between ovarian volume determined by ultrasound and age.[10,22] In our study, the nonsignificant decline in ovarian volume with age might be due the presence of 20% of women with postmenopausal vaginal bleeding, diagnosed as endometrial adenocarcinoma and who had significantly large-sized ovaries. There is an elevated risk of endometrial cancer among elderly women at menopause,[23] as observed in our study; the women with endometrial adenocarcinoma had a significantly higher menopausal age compared with other histologic groups.

The finding that obesity is associated with increased endometrial cancer is well established.[23] The present results revealed a significant association between large ovaries and higher BMI; this was in accordance with others.[9,10] Obese women (BMI ≥30) are well known to have insulin resistance and compensatory hyperinsulinemia, which play a role in the ovarian enlargement observed in these women.[9,24] The larger ovarian volume among postmenopausal women was associated with an increased risk of endometrial cancer and has been shown to be greatest for women with large ovarian volume.[10,25] This was consistent with our findings that endometrial adenocarcinoma was significantly associated with larger-sized ovaries relative to other histologic groups.

Increased ovarian volume and relatively high serum concentration of estrogens and free testosterone in postmenopausal women were associated with an increased risk of endometrial cancer.[23,25] This observation was confirmed by our findings that large ovaries in postmenopausal women with endometrial adenocarcinoma was associated with significantly increased serum levels of estradiol, free testosterone and total testosterone. A large recent prospective study that showed that circulating blood levels of estrogens, free testosterone and to a lesser extent total testosterone are positively associated with an increased risk of endometrial cancer in postmenopausal women, also suggested that free testosterone may be an important determinant of endometrial cancer risk in postmenopausal women and that this association could be a result of peripheral conversion of these androgen to estradiol.[23]

In conclusion, our analysis suggest that enlarged ovaries in women with postmenopausal bleeding and thickened endometrium are associated with endometrial adenocarcinoma risk and represent a marker of the availability of the androgens for peripheral estrogen synthesis, whereas obesity affects the degree of conversion.

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Chyluria: a mimicker of nephrotic syndrome

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BACKGROUND AND OBJECTIVE: Chyluria can be confused with nephrotic syndrome when massive proteinuria is present on urine examination during evaluation of a milky/white urine. Our objective was to attempt to resolve diagnosis in the case of nephrotic range proteinuria when there is no clear evidence of a significant kidney lesion.
DESIGN AND SETTING: Retrospective review of the medical records of all patients referred the nephrology department at a single institution.
PATIENTS AND METHODS: We identified a subgroup of patients misdiagnosed with nephrotic syndrome and treated aggressively with immunosupression with no benefit and who were later diagnosed as having chyluria.
RESULTS: Twelve patients were identified (8 men, 4 women) with a median age of 34.5 years. Chyle was positive in the urine in eight while chyle was positive on oral ingestion of butterfat in another 4. Six had undergone kidney biopsy and were treated as having minimal change disease. Eight had massive proteinuria and a history of treatment with prednisone, but none of these patients had shown improvement in their clinical presentation. Two patients showed excellent results with diethylcarbamazine with angiotensin-converting enzyme inhibitors in while eight required betadine instillation in the fistulous connection with success in six. Surgical correction was successfully tried in two of these resistant cases.
CONCLUSION: In individuals with nephrotic range proteinuria with a normal or low lipid profile status along with normal serum albumin levels, urine color and nature, frequency, and checking the urine for chyle can help identify the large subgroup who unnecessarily have to undergo kidney biopsy and at times are treated with immunosuppression, which is not only life threatening but useless in these patients.

Chyluria is defined as the passage of chyle into the urine. Chyle is comprised of large quantities of dietary lipids, proteins and fat soluble vitamins. Chyluria occurs when there is an abnormal communication between the lymphatic and urinary systems. Chyluria can be confused with nephrotic syndrome when massive proteinuria is present on urine examination during evaluation of milky or white urine. At times it becomes more difficult when patients present with nephrotic range proteinuria and active sediments, but lack of edema, normal serum albumin and an abnormal or normal lipid profile may alert physicians to nephrotic syndrome and the need for kidney biopsy and aggressive treatment with potentially harmful immunosuppression, with no benefit. We report a series of such cases when chyluria was confused with nephrotic syndrome and the patients subjected to kidney biopsy and immunosuppression or both. The idea was to resolve situations where an individual presents with nephrotic range proteinuria without any clear evidence of a significant kidney lesion or other explanation of the massive amount of protein leak from the kidneys.

PATIENTS AND METHODS

We retrospectively identified the records of all patients referred to the Department of Nephrology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, for evaluation of nephrotic syndrome, which on further evaluation was determined to be chyluria.

RESULTS

Twelve patients were referred for evaluation of nephrotic syndrome and later diagnosed with chyluria. Eight were men with median age of 34.5 years (**Table 1**). Not all patients had a prominent history of passing "white

Table 1. Twelve patients referred for evaluation of nephrotic syndrome.

Median age (years)	34.5
Age range (years)	31-44
Sex (M:F)	8:4
Continuous turbidity of urine	4
Intermittent turbidity of urine	4
History of no turbidity of urine	4
History of filarial infection	2
History of renal colic or passing of clots	2
Positivity of urine for chyle (random)	8
Positivity of urine for chyle after fat ingestion	4
Urine test for acid-fast bacilli	Negative in all
24-hour proteinuria (3-10 g/d)	6
24-hour proteinuria (>10 g/d)	6
Patients subjected to kidney biopsy	6

Values are number of patients unless noted otherwise.

Table 2. Clinical profile including side effects due to immunosuppression in the 12 patients.

Variable	Number of patients
History of usage of steroids	6
History of usage of other immunosuppressive agents	2
Cushingoid facies	4
Infection	2
Hypertension	3
Diabetes mellitus	1
Response to therapy[a]	
Diethylcarbamazine + ACE inhibitors	6/6
Betadine instillation	6/8
Surgical correction	2/2

[a] Positive response/number treated.

urine", but they had no anasarca, normal lipid profiles and serum albumin, and the urine was either positive or normal for chyluria. Urine tests for acid-fast bacilli were negative in all patients. Chyle was positive in the urine in 8 while another 4 were positive for chyle on oral ingestion of butterfat. Six of these patients had undergone kidney biopsy before being referred to us and were treated as having minimal change disease based on normal light microscopy changes. Eight had massive proteinuria and a history of treatment with immunosuppression, and none had shown improvement in clinical presentation. The condition was responsible for serious infection in two patients and worsening of hypertension in 3 (**Table 2**). Retrograde pyelography demonstrated the fistulous connection and dilated lymphatics in four patients while lymphangiography was the diagnostic modality in another four. Six of the patients showed a response to diethylcarbamazine and angiotensin-converting enzyme (ACE) inhibitors. Betadine instillation was successful in six of eight patients who had not responded to conventional treatment, all of whom were in remission. Chyluria did not resolve in two patients after two instillations of betadine, and open surgical ligation and excision of the renal pedicle lymphatics was tried with significant success (**Table 2**).

DISCUSSION

The clinical suspicion of chyluria was raised in these 12 patients who initially presented as having nephrotic syndrome (all had proteinuria >3 g in 24 hours) and a history of continuous or intermittent turbid urine, but with no stigmata of the clinical syndrome. After testing for chyle in urine, eight patients were positive while another four tested positive on challenge with dietary fat. A kidney biopsy was attempted in six patients, which was later reported as normal with some suggestion of minimal change disease. Eight of these 12 patients were treated with immunosupression, which resulted in serious infections in two patients. Treatment options tried were diethylcarbamazine with ACE inhibitors in two with excellent results, while eight required betadine instillation in the fistulous connection with success in six. Surgical correction was successfully tried in two of these resistant cases.

Chyluria may be associated with dysuria or hematuria due to rupture of small blood vessels adjacent to the fistulous communication.[1-5] Individuals can at times present with anemia, hypoproteinemia due to loss of protein, and fat in the urine subsequent to weight loss and malnutrition.[6,7] However, usually these individuals are clinically asymptomatic as was evident in our study population where, despite documented proteinuria >3 g/24 hours with active urinary sediments, none of these individuals showed any evidence of gross anascarca, hypoproteinemia or lipid abnormalities that clinically aroused a suspicion of a nonglomerular pathology for this massive proteinuria. Chylous clots may cause renal colic and obstruction, which is significant when the stigmata of classical nephrotic syndrome are not present and after ruling out other systemic causes. On repeated questioning, two patients admitted a history of turbid urine, hematuria and at times clots, which are never present in patients with classical nephrotic syndrome.

Clots rule out nephrotic syndrome.

Once a clinical diagnosis of a nonglomerular cause for proteinuria and hematuria is made, the investigations necessary for chyluria are intravenous pyelography, cystoscopy, retrograde pyelography and lymphangiography. Retrograde pyelography can demonstrate the fistulous connection and dilated lymphatics,[8] which was used to diagnose the fistulous communication in four of our patients. Lymphangiography, which can clearly demonstrate the lymphopelvic fistulous communication[9] was used to diagnose chyluria in another four patients. Genitourinary tuberculosis should be considered in the differential diagnosis and a urine test for acid-fast bacilli is necessary to rule out tuberculosis in a country like India. All our patients had a negative urinary acid-fast bacilli report.

The natural history of chyluria is still not clear. Spontaneous remission can be observed in 50% of cases so not all require treatment. When chyluria presents with proteinuria, a favorable outcome has been reported following treatment with ACE inhibitors.[10] Six patients in our study group showed a response to diethylcarbamazine and ACE inhibitors, but this could also be because of spontaneous remission. Sahoo et al in their study were able to show similar results as proteinuria resolved after treatment with diethylcarbamazine and ACE inhibitors. Surgical management is indicated in refractory severe chyluria with recurrent clot colic and urinary retention.The available surgical techniques are endoscopic sclerotherapy, surgical lymphatic disconnection and microsurgeries. Instillation of AgNO3 or even betadine[11] has been used and is considered to be a safe effective and a minimally invasive procedure with an initial success rate of about 70% to 80% and a long-term recurrence rate of 50%. However, in eight of our patients betadine instillation showed significant success with remission in six. Another two underwent open surgical ligation and excision of renal pedicle lymphatics with significant success following repeated betadine instillation.

Sahoo et al screened 282 cases of Bancroftian filariasis over a period of 7 years and found 42 cases with proteinuria over 150 mg/24 h.[12] Light microscopic examination of renal biopsy tissue from 27 patients revealed predominantly mesangioproliferative changes in 18 cases and endocapillary proliferation in 9 cases. Basement membrane thickening and tubular degeneration were observed in six cases each. Immunofluorescence showed mesangial deposits of IgG alone, or in combination with C3 in 12 patients, and granular deposits of IgG and C3 along capillary wall in three patients, suggesting immune-mediated glomerulopathy/filiarial nephropathy. However, in our kidney biopsy specimens we were able to appreciate only focal and mild effacement of visceral epithelial cell foot processes without electron dense deposits, thus suggesting a glomerular and nonglomerular association with filiarial infection.

In conclusion, in nephrotic-range proteinuria with a normal or low lipid profile status along with normal serum albumin levels, a careful history is mandatory to determine the color of the urine, its nature and frequency of urination. Checking the urine for chyle can help reduce a large subgroup of these patient who unnecessarily undergo kidney biopsy and at times are treated with immunosuppression, which is not only life threatening but useless in chyluria.The degree of proteinuria and its association with chyluria is still under evaluation. This question needs to be answered in future large-scale studies.

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original article

Childhood onset of Crohn disease: experience from a university teaching hospital in Saudi Arabia

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BACKGROUND AND OBJECTIVES: Crohn disease (CD) is an increasingly recognized problem in Saudi Arabia. The aim of this study was to describe the clinical pattern in children and adolescents with CD seen at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia.

DESIGN AND SETTING: Retrospective hospital-based study conducted on data collected for the period between January 2001 and March 2010.

PATIENTS AND METHODS: Data for all children and adolescents diagnosed at KAUH with CD in the period were retrieved and analyzed.

RESULTS: Ninety-six patients were identified. The median age at diagnosis was 11.3 years (range, 0.12-17.6 years). Fifty (52.1%) were males. Sixty-four (66.7%) were Saudis. Nine (9.4%) had a first degree relative with inflammatory bowel disease. The most common presenting symptoms were diarrhea (88.5%), weight loss (84.2%) and anorexia (80.2%). At least one extraintestinal manifestation occurred in 24% of patients. Forty-two percent were underweight and 19% had short stature. The most common distribution was ileocolonic (37.5%), followed by colonic in 31.2%. Twenty-five (26%) patients had perianal disease, 13 (13.5%) had strictures and 15 (15.6%) had penetrating disease. Laboratory investigations revealed anemia in 84.4%, thrombocytosis in 50%, hypoalbuminemia in 64.6%, elevated erythrocyte sedimentation rate (ESR) in 50% and elevated C-reactive protein in 58.3%. Induction of remission was achieved with enteral nutrition in 20% of patients and with corticosteroids in the remaining.

CONCLUSIONS: The clinical pattern of CD in children from the Western Province of Saudi Arabia was found to be similar to reports from the West. Pediatricians should be aware of the varying presentations of CD. Early referral to specialized centers is crucial.

Inflammatory bowel disease (IBD) comprises Crohn disease (CD) and ulcerative colitis (UC), both lifelong chronic inflammatory conditions of the gastrointestinal tract arising in previously healthy individuals. Up to 25% of patients with IBD first present in childhood. The underlying etiology and pathogenesis of IBD remain largely unknown, but it is thought to result from an interaction between genetic susceptibility, environmental factors and the host immune response. CD is traditionally described as a patchy inflammation affecting any part of the gastrointestinal tract from mouth to anus, with discontinuity in affected areas. CD can affect all layers of the gastrointestinal tract and can proceed to strictures or fistula.[1,2]

IBD has been regarded as a disease primarily occurring in Western populations.[3,4] It was thought that IBD was rare or nonexistent in Saudi Arabia.[5] The first reported case of CD in Saudi Arabia was in 1982.[6] Since then there have been many reports of CD of adults in Saudi Arabia from different regions, including both urban and rural areas.[7,8] There has been a marked global increase in the incidence of IBD, particularly in pediatric populations.[9] There are reports of an increase in CD among children in Saudi Arabia. Toonisi[10] and El

Mouzan et al[11] reported the occurrence of CD in 17 and 19 children respectively. The aim of our study was to describe the clinical pattern in children and adolescents with CD attending the pediatric gastroenterology clinic at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia in the period between January 2001 and March 2010.

PATIENTS AND METHODS

We conducted a retrospective study of all children and adolescents with CD seen at KAUH between January 2001 and March 2010. A list of patients was generated by accessing the ICD-10 codes of the hospital admissions database. This data was augmented with data from an endoscopy unit database to ensure that all possible patients during the study period were included. Patients with CD were selected from the list of patients with IBD, where chronic inflammation of all or part of the digestive tract was documented. The diagnosis of CD was made in accordance with ESPGHAN Porto Criteria.[12] Relevant clinical and demographic information from all identified patients was recorded. Colonic infections were excluded by repeated stool examination and culture.

TB was excluded on the basis of a detailed family history, imaging studies, a negative purified protein derivative (PPD) test result and a negative PCR- hybridization of *Mycobacterium tuberculosis* on biopsy tissue obtained during colonoscopy. Follow up information for disease progression and outcome were retrieved from patients' charts. The anatomical extent of CD was determined by the initial colonoscopy, upper endoscopy and radiological studies. The distribution of CD was defined according to the Vienna classification where L1 stands for ileal, L2 for colonic, L3 for ileo-colonic, and L4 for disease in the upper gastrointestinal tract. The behavior of the disease was classified into B1 for non-stricturing non-penetrating, B2 for stricturing and B3 for penetrating disease.[13] Clinical remission of the disease was defined as the disappearance of clinical symptoms with normalization of the inflammatory markers including CRP and ESR.

The z scores for weight and height were calculated by using an anthropometric software program (Epi-Info, Centres for Disease Control and Prevention, Atlanta, GA, USA). Statistical analyses were performed using SPSS 19 software (IBM Corp, Armonk, New York, United States). Data were expressed as percentage of the total for categorical variables, as mean with standard deviation (SD) for normally distributed continuous variables, or as median with interquartile range for skewed distributed variables. A comparison of study groups was performed using the chi-square test for variables. All statistical analyses utilized a .05 level of significance. This study was approved by the Research Ethics Board at KAUH.

RESULTS

From January 2001 to March 2010, 157 children and adolescents with the diagnosis of IBD were identified at KAUH. Ninty-six patients were diagnosed with CD, which constituted 61.5% of the total IBD cases. The diagnostic modalities performed for these patients are shown in **Table 1**. The number of new CD cases diagnosed each year is presented in **Figure 1**. The median age at diagnosis was 11.3 years (range, 0.12-17.6 years). The age distribution is shown in **Figure 2**. Fifty (52.1 %) were males. Sixty-four (66.7%) were Saudis, while 24 (25%) were non-Saudis and 8 (8.3%) were nonArabs. First-cousin type consanguinity was present in 20 (35%) of the cases. A family history of IBD was present in 9 (9.4%) patients. Eight had affected siblings (7 had CD and 1 had UC) and 1 had an affected parent with UC. The concordance rate for CD was 78%.

The presenting symptoms are shown in **Table 2**. The median duration of symptoms prior to presentation was 8 months (range, 1-48 months). The most common extra-intestinal manifestation (EIM) observed was oral manifestations that occurred in 18 (18.6%) patients. Oral manifestations included angular cheili-

Table 1. Diagnostic modalities in the 96 patients.

	Number	Abnormal findings, n (%)
Endoscopy		
Colonoscopy with ileal intubation	90	88 (98)
Colonoscopy without ileal intubation	6	6 (100)
Upper endoscopy	27	4 (15)
Imaging		
Barium meal and follow through	66	49 (74)
Small bowel enema (enteroclysis)	13	11 (85)
CT scan with contrast	16	13 (81)
MRI	7	4 (57)
Histopathology		
None caseating granuloma	21	(22)

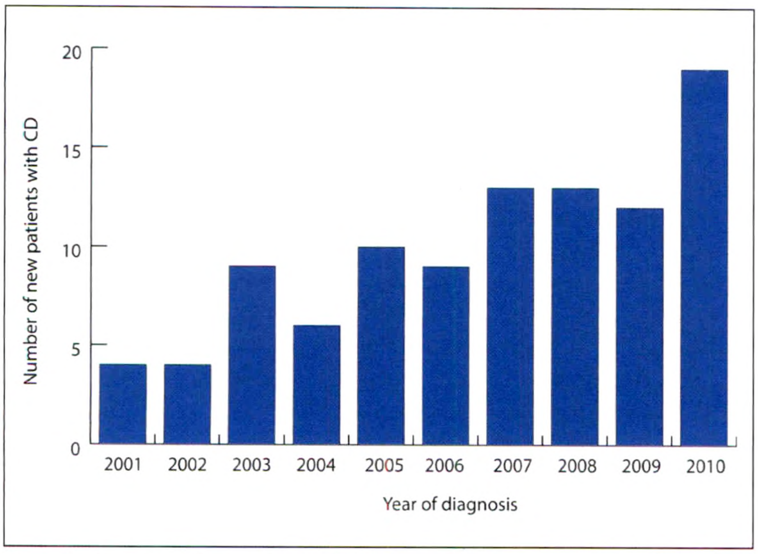

Figure 1. The number of new cases of Crohn disease diagnosed each year.

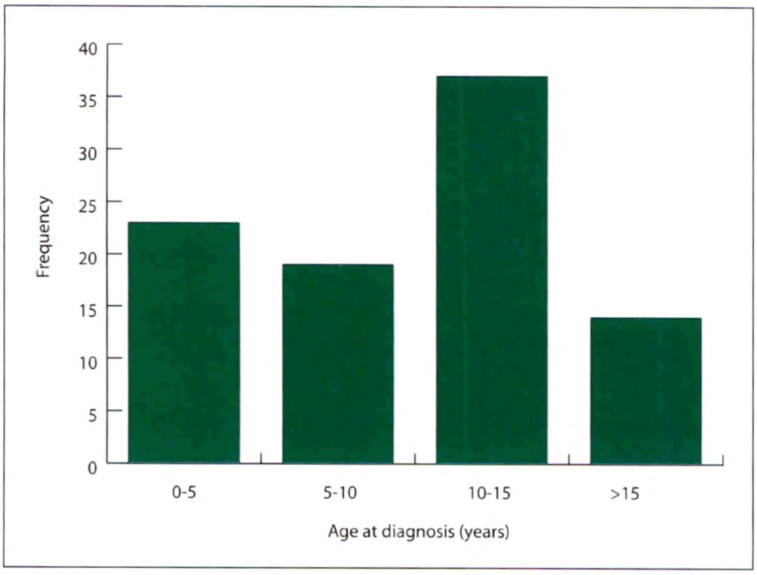

Figure 2. The age distribution at the time of CD diagnosis (n=96).

tis (n=9), apthous ulcerations (n=7), deep ulcerations of the tongue (n=3), mucogingivitis (n=2) and linear ulcerations of the buccal mucosa (n=2). There was no association between the type of oral involvement and either the disease phenotype or the presence of perianal disease (chi-square, P=.16 and P=.14 respectively). Two patients suffered from eye involvements, one had uveitis and the other had keratitis. Two (2%) had concomitant type-1 autoimmune hepatitis. Both had elevated transaminases at diagnosis. The diagnosis was confirmed by positive serology for anti-smooth muscle antibody compatible liver histopathology and normal magnetic resonance cholangiopancreatography. Both responded to treatment with corticosteroids. One patient had peripheral arthritis and one had skin vasculitis.

Lung involvement was observed in a 15 year-old girl who presented with chronic cough, diarrhea and weight loss. Her chest x-ray showed bilateral patchy alveolar opacities affecting mainly the upper lobe with increased mediastinal shadow. Chest CT scan showed a prominent right hilar lymph node and patchy areas of consolidation more seen in the right lung apex with bilateral scattered ill-defined confluent air space-opacities scattered in both lung fields. Workup for TB and immunodeficiency was negative. In spite of treatment with appropriate antibiotics she continued to have persistent symptoms and radiological abnormalities. Her lung condition resolved completely following the diagnosis and treatment with corticosteroid followed by maintenance with azathioprine.

At diagnosis, the median weight for age z-score was -2.26 (range, -11.6 to 2.3), while the median height for age z-score was -1.52 (range, -9 to 1.28). Forty-two percent had weight for age z-score less than -2.5 and 19% had height for age z-score less than -2.5. The median body mass index (BMI) z-score was -1.1 (range -10.4 to 9.6). 35% of patients had BMI z-scores less than -2.5. The difference between the means of weight and height z-scores between patients with different disease locations was not statistically significant (ANOVA, P=.78 and P=.52 respectively) which indicates that growth is equally affected regardless of the disease distribution.

The disease phenotype according to Vienna classification is shown in **Table 3**. The most common distribution was ileocolonic. Gastric involvement occurred in four patients, but isolated gastric involvement was seen in only one patient. An isolated colonic distribution occurred more frequently in younger children, while ileal and ileocolonic involvement occurred more frequently in older children. The mean age (SD) for the group with isolated colonic involvement (n=33) vs. the mean age (SD) for the group with ileal involvement (n=62) was 6.7 (5.3) vs. 11.3 (4.2), P<.001.

Twenty-five (26%) patients reported in this series had perianal disease other than perianal fistulae. Perianal disease varied from isolated skin tags to severe perianal ulceration. Chronic multiple anal fissures were diagnosed in 15 patients. Skin tags were present in 12 patients. Three had isolated skin tags, while 4 had severe ulcerations in the natal cleft and 3 had perianal abscesses. Perianal disease was the only presenting sign in

Table 2. Presenting symptoms in the 96 patients with Crohn disease.

Symptoms	Number	Percentage
Diarrhea	85	88.5
Weight loss	81	84.4
Anorexia	77	80.2
Abdominal pain	74	77
Passage of mucus	37	38.5
Bleeding per rectum	35	36.5
Fever	28	29.2
Vomiting	20	20.8
Tenesmus	10	10.4

Table 3. The disease phenotype according to Vienna classification (n=96).

	Number	Percentage
Location		
Ileal (L1)	29	30.2
Colonic (L2)	30	31.3
Ileo-colonic (L3)	36	37.5
Upper gastrointestinal (L4)	1	1
Behavior		
Non-stricturing non-penetrating (B1)	68	70.83
Stricturing (B2)	13	13.54
Penetrating (B3)	15	15.63

two (2%) patients.

Strictures were identified in 13 (13.5%) patients. These strictures were inflammatory, affecting only the small bowel. Eleven patients had involvement of both proximal and distal ileal loops. Three had jejunal strictures and two had distal duodenal strictures. The stricturing complications were associated with small bowel disease (chi square, *P*=.04). Penetrating complications occurred in 15 (15.6%) patients, presenting with perianal fistulae in 11 and internal fistulae in 4 patients. The internal fistulae were ileo-ileal (n=2), ileo-sigmoid (n=1) and ileo-vesical (n=1). Penetrating complications were not correlated with disease location (chi square, *P*=.7).

Eighty-one (84.4%) patients were anemic at diagnosis with a mean (SD) hemoglobin level of 10.2 (1.6) g/dL (normal, 12-14.5 g/dL). Thrombocytosis was present in 48 (50%) patients with a mean (SD) platelet count of 664 (193)×10^3/μL (normal, 150-450×10^3/μL). Sixty-two (64.6%) patients had low albumin with a mean (SD) albumin level of 25 (7.2) g/L (normal, 35-50 g/L). The erythrocyte sedimentation rate (ESR) was high in 48 (50%) of 70 patients tested (normal, 0-15 mm/hr), while C- reactive protein (CRP) was abnormally elevated in 56 out of 80 (58.3%) patients (normal, 0-3 mg/L).

Induction of remission was achieved in 80 (83%) patient using oral prednisolone in a dose of 1-2 mg/kg/day (maximum 40 mg/day) for 4 weeks followed by a gradual reduction of the dose for 4-8 weeks depending on the response. Remission was successfully induced using only enteral nutrition in 16 of 50 patients in whom this modality of therapy was attempted. Enteral nutrition was given as liquid polymeric formula for 6 weeks followed by gradual and slow introduction of solid food. These formulas were delivered through a nasogastric tube in 13 patients and orally in 3 patients.

Azathioprine was used for maintenance of remission in almost all patients in addition to 5-amino salicylic acid derivatives (mesalazine). The usual dose for azathioprine was 2-2.5 mg/kg/day, while the dose for mesalazine was about 50-100 mg/kg/day as tolerated. Thirty patients required biological therapy using infliximab (n=22) or adalimumab (n=8). Patients who were candidates for biological therapy were routinely screened for TB using the tuberculin skin test and a chest x-ray. Also, prior to treatment, they were screened for hepatitis B and C viruses and HIV.

Infliximab was given as intravenous infusion in a dose of 5 mg/kg/dose at 0, 2 and 6 weeks for induction followed by treatment every 8 weeks as maintenance. Adalimumab was given subcutaneously in a dose of 80 mg initial followed by 40 mg every other week for younger children or at the initial dose of 160 mg followed by 80 mg every other week for adolescents. Patients were evaluated after 12 months of treatment and a decision was made with the family whether to continue or to stop treatment at that stage. The indications for biological therapy in this cohort were 1) perianal and fistulizing disease, 2) failure of conventional treatment using azathioprine and 5-aminosalysylate as maintenance therapy with frequent relapses requiring repeated courses of corticosteroids or 3) extensive disease causing severe growth failure.

Surgery was required for 8 (8.3%) patients. Three had diversion colostomy for severe perianal disease, one had resection of inflammatory mass at the terminal ileum and cecum with anastomosis, one had repair of the internal fistula into the urinary bladder, one had repair of a perforated colon, one had drainage of an intra-abdominal abscess, and one had deep gluteal abscess drainage.

The mean (SD) duration of follow up was 3 (2.8) years, range from 0.15 to 12 years. Twenty-nine (30%) patients were lost to follow up. All patients treated with corticosteroids were steroid responsive. Eleven (11.5%) were steroid dependent. Fifty-six (58.3%) patients had one or more relapses during follow up. The median number of relapses per year was 0.67 (range, 0.1 to 6.55 relapses per year).

DISCUSSION

CD is becoming more prevalent than UC with a greater percentage of patients presenting during childhood.[14] In this series, CD comprised 61.5% of the total IBD cases diagnosed during the study period. There was a significant increase in the number of new cases every year as shown in **Figure 1**. This observation confirms a previous report.[11] It is debatable whether this is due to lack of diagnostic facilities and trained medical personnel or whether the disease incidence is truly increasing. It has been suggested that marked socioeconomic development experienced in Saudi Arabia over the years has not only lead to an improvement of health services in general, but also has been associated with a clear change towards a more Westernized lifestyle.

In this study a significant number of patients were infants (**Figure 2**). The development of IBD in infancy is extremely rare. Published data from epidemiological studies and IBD registries in North America and Europe suggest that less than 1% of children with IBD present during the first 12 months of life.[15,16] In contrast to older children, almost all infants with IBD have disease involving the colon. Additionally, there may be a higher prevalence of perianal involvement in this age group.[17]

In line with the high rate of consanguineous marriages in Saudi Arabia,[18] we found a high rate of first-cousin consanguinity in this study. We also found a family history of IBD affecting first-degree relatives in 9 (9.4%) patients. This rate of family clustering with IBD is close to the rate of 10.9% seen in 129 Greek children with CD reported by Roma et al.[19] In our study the concordance rate for the clinical phenotype of the disease was 78%. This is higher than the concordance rate of 58.3% in children with CD reported in the study by Roma et al.[19]

IBD may be complicated by EIMs. Six percent of pediatric patients had at least 1 EIM before diagnosis with IBD. At least 1 EIM will develop in 29% within 15 years of diagnosis.[20] In our cohort oral manifestations were the most common. This frequency is less than the 48% reported in a study from Dublin.[21] The most common lesions found in our study were angular stomatitis and aphthous ulcerations. In another study with Italian adults angular cheilitis was the most frequent oral manifestation,[22] other investigators have reported mucogingivitis and cobblestoning as being the most frequent oral lesions.[21,23] Tongue involvement in CD has been rarely reported as an isolated manifestation,[24] or part of the rare Melkersson-Rosenthal syndrome which is associated with orofacial swelling and relapsing facial paralysis.[25] Our patients had isolated tongue involvement with deep ulcerations with loss of tissue causing irregularities at the margins of the tongue that healed after treatment with immunosuppressive therapy.

Liver involvement in the form of type-1 autoimmune hepatitis occurred in two (2%) patients. Nemeth et al[26] reported mild pathological liver function in 4 (33%) of 12 pediatric patients with CD. Also, Hyams et al[27] reported chronic active hepatitis in less than 1% in children with either CD or UC, while sclerosing cholangitis was reported in 3.5% of UC patients and less than 1% of CD patients. None of our patients had sclerosing cholangitis. Both patients described in the current study responded well to treatment with corticosteroids with normalization of their liver function tests and subsequently maintained on low dose of corticosteroids.

The development of stricturing and penetrating disease are among the important complications of CD diagnosed during childhood and adolescence. In our patients stricture complications were associated with small bowel disease in line with other studies.[28,29] However, penetrating complications were not found to be associated with the disease location in contrast to some other investigators who have reported an association between penetrating complications and colonic disease,[30,31] while others reported an association between penetrating complications and small bowel CD.[32,33]

The medical treatment of newly diagnosed CD patients included induction of remission followed by maintenance and prevention of relapse. In addition to corticosteroids, enteral nutrition therapy is established as a valid and effective treatment in pediatric CD. Some studies have shown that enteral nutrition is comparable to corticosteroids in achieving remission.[34] One additional advantage of using enteral nutrition is the induction of mucosal healing.[35,36] In our cohort of children with CD, we were able to use enteral nutrition successfully in only one-third of patients who attempted enteral nutrition. The difficulties encountered in using enteral nutrition were related mainly to compliance, especially in the adolescent age group. Other factors which may have worked against the success of enteral nutrition could have included lack of access to dietetic support and lack of financial support for the provision of such expensive formula.

Biological therapy in the form of anti-tumour necrosis factor alpha (anti-TNF-α) was considered in a selected group of patients with moderate to severe CD, particularly in those with perianal and fistulizing disease in whom other medical therapies were often unsuccessful. Infliximab and adalimumab are the most commonly used anti-TNF-α agents for the treatment of patients with moderate to severe CD.[37-39] In this cohort, 30 children were successfully treated with biological therapy using infliximab or adalimumab.

In conclusion, this study has shown that the clinical characteristics of CD including the disease phenotype and behavior, in children in the Western Province of Saudi Arabia are generally similar to those reported from the Western population. Pediatricians should be aware of various presentations of CD since early recognition of the disease and timely medical treatment helps in achieving control of the disease and avoids its complications.

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Metabolic syndrome components in obese Egyptian children

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BACKGROUND AND OBJECTIVES: Obesity is one of the most serious global health issues. The aim of this study was to assess the association between obesity and different components of metabolic syndrome among obese school children aged 7 to 9 years, and to identify associated clinical and biochemical characteristics.

DESIGN AND SETTING: Case-control study among children attending Al-Zahraa Hospital Outpatient Clinic March 2010.

SUBJECTS AND METHODS: The study included 60 obese children (28 boys and 32 girls) and 50 non-obese controls (25 boys and 25 girls). Anthropometry, fasting glucose, insulin concentrations, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides, systolic and diastolic blood pressure (BP) were measured. Insulin resistance was determined by Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). Subcutaneous and visceral fat thicknesses were measured ultrasonographically. Metabolic syndrome (MS) was defined according to the Cook criteria.

RESULTS: MS was found in 25% of obese cases. Obese children showed significantly higher values in waist circumference, waist-to-hip ratio, levels of systolic and diastolic BP, insulin, HOMA-IR and LDL compared to their lean controls. HDL was significantly lower in obese children compared to controls. Obese children with MS had significantly higher values of body mass index standard deviation score (SDS), skinfold thickness, visceral fat thickness, waist circumference, systolic and diastolic BP, HOMA-IR, insulin and triglycerides compared to obese children without MS, whereas HDL was significantly lower. Obese children with MS had a high prevalence of hypertension and dyslipidemia compared to children without MS. Results showed positive relationships between visceral fat and waist circumference as well as with insulin level in obese children ($P<.05$).

CONCLUSIONS: The prevalence of the MS is considerable among obese Egyptian children. Abdominal obesity and high HOMA-IR values were the most frequent components of this syndrome among obese children. The study suggests that increased degree of insulin resistance is associated with a heightened risk of suffering MS.

The prevalence of chronic or noncommunicable diseases is escalating much more rapidly in developing countries than in industrialized countries. According to WHO estimates, by the year 2020, noncommunicable diseases will account for approximately three quarters of all deaths in the developing world.[1] The prevalence of overweight and obesity among schoolchildren aged 6 to 10 years in the Eastern Mediterranean Region was 12% to 25%. Many developing countries, including the Middle East, have undergone epidemiologic and demographic transitions affecting their population's nutritional status and created environments that contribute to an increase in obesity, a health problem that often coexists with undernutrition in this type of nation.[2] As a major risk factor for chronic disease, the metabolic syndrome (MS) is rapidly increasing in prevalence with rising childhood obesity and sedentary lifestyles worldwide. Few studies have estimated the prevalence of metabolic syndrome in children, and no international definition exists.[3] Studies from the past years have reported an alarming increase in the prevalence of the MS among children and adolescents.[4,5] The MS is an aggregation of abnormalities in lipid and carbohydrate metabolism accompanied with hypertension, all of which are risk factors for cardiovascular disease.[4,6] Genetic predisposition or early-life adverse events may contribute to the insulin resistance and adverse body-fat patterning seen in MS and its related complications. MS is closely associated with obesity, especially with central distribution. Parameters associated with MS have been shown to originate early in life[7] and tend to track into adulthood.[3] The recognition of MS in obese children, who have not yet developed cardiometabolic disorders, is of great importance from a clinical and public health perspective.[8] Many studies have shown that high levels of body mass index (BMI) among children and adolescents were associated with adverse levels of lipids, insulin, and blood pressure, all components of the metabolic syndrome.[4,9] Insulin resistance (IR) and an altered plasma lipid pattern are common pathophysiological features of MS, not only in adults but also in children and adolescents.[9] The MS has been widely studied in adults, but there is little research focusing on younger children (<10 years old).[10] Moreover, the absence of studies on MS in the pediatric Egyptian population led us to design the current study. The aim of this study was to assess the association between obesity and the different components of MS among obese Egyptian schoolchildren aged 7 to 9 years old, and to identify clinical and biochemical characteristics associated with MS in our population.

SUBJECTS AND METHODS

We conducted a case-control study during March 2010. The subjects of this study comprised 110 children: 60 were obese (28 boys and 32 girls) and 50 were non-obese, normal healthy controls randomly chosen from both sexes (25 boys and 25 girls). All were attending the Pediatric Clinics of Al-Zahraa Hospital, Al-Azhar University, Cairo, Egypt. Their ages ranged from 7 to 9 years. A formal consent letter from the parents of each child included in the study was obtained after explaining the study to them. This study was approved by the Ethics Committee of the hospital. The nutritional diagnosis of obesity (BMI equal to or higher than the 95th percentile) was performed according to age and gender.[11] The obese children with a clinical history of other morbidities and undergoing medical treatment and clinical-nutritional follow-up for body weight reduction were excluded.

The anthropometric measurements and instruments followed the International Biological Programme (IBP).[12] Measurements were taken three times and the mean values used in the analysis included weight, height, waist and hip circumferences, triceps and subscapular skinfold thicknesses. Body weight was measured to the nearest 0.1 kg and height was measured to the nearest 1 mm. The skinfold thickness was measured to the nearest 1.0 mm. The triceps skinfold was measured parallel to the long axis of the arm midway between the acromion and the olecranon, with the arm slightly flexed, and the subscapular skinfold was measured below the lower angle of the left scapula at a diagonal in the natural cleavage of the skin. BMI in kg/m^2, and waist-to-hip ratio (WHR) were calculated. Age was calculated in decimal units based on the date of the examination relative to birth date. Physical growth was assessed for each child by determining the standard deviation scores (SDS) of weight, height, BMI, using the Egyptian growth reference data.[11] The SDS was calculated independent of sex and age that is, child measurement minus population mean/population SD. WHR ratio was also calculated and compared to the control group in the present study.

Medical assessments were performed, including a history of symptoms covering various systems, and a physical examination was performed looking for characteristic abnormalities, specifically acanthosis nigricans. Blood pressure was measured by the auscultatory method after the child had been sitting at rest for a minimum period of 5 minutes, and the cuff involved 80% of the right arm circumference. The arm rested on a support surface at the level of the precordium. Blood pressure was measured three times and was averaged for analysis. Blood pressure was measured three times in three different days only when the first measurement was above 95th percentile according to gender, age and height, based on The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.[13] Fasting plasma glucose and serum lipids (total cholesterol, HDL, LDL, triglycerides) were measured by enzymatic colorimetric methods using a Hitachi autoanalyzer 704 (Roche Diagnostics. Switzerland).[14] Serum insulin concentration was analyzed by chemiluminescent immunoassay (Immulite 2000, Siemens, Germany).[15] Insulin resistance was then determined by the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) calculated as the product of the fasting plasma insulin level (μU/mL) and the fasting plasma glucose level (mmol/L), divided by 22.5.[16] We used the Cook definition for MS,[17] which includes the presence of >3 of the following five conditions: (1) central obesity (waist circumference (WC) >90th percentile)[18] (2) fasting triglycerides >110 mg/dL, (3) HDL <40 mg/dL, (4) blood pressure >90th percentile for age, gender and height, and (5) fasting glucose >100 mg/dL.[17]

Ultrasonography (US) measurements of subcutaneous and visceral abdominal fat layers were performed using a 7.5 MHz linear-array probe; the rectus muscle to spine and rectus muscle to aorta distances was measured as indicative of visceral fat thickness, and the distance between skin to fat and fat to rectus muscle interfaces was indicative of subcutaneous fat thickness using VIVID Three (GE, Healthcare, United States) ultrasound scanner with a high resolution B-mode.[19]

Statistics were done by computing the mean and standard deviation (SD) for scale variables, or frequencies for nominal variables. To study the independence between nominal categorical variables the chi-square test was used. An independent samples t test was performed on scale variables to evaluate the differences between two groups. The normality of scale variables was assessed using the Kolmogorov-Smirnov test. The Mann-Whitney test was used in ordinal variables to evaluate the differences between two groups. A HOMA-IR value of 3.4 was chosen as the cut-off point to define IR as it has been suggested that beyond this value, which corresponds to the 90th percentile of a population of healthy children, IR becomes a cardiovascular risk factor. Four categories were used for HOMA-IR percentiles: <25th, 25-49.9th, 50-74.9th, and ≥75th, to assess the risk of developing MS through logistic regression analysis. Statistically significant differences were assumed if the *P* value was <.05. Statistical presentation and analysis of the results were carried out using SPSS software version 11.

Table 1. Anthropometric, clinical and biochemical characteristics of the obese children, according to gender.

Features	Boys Mean (SD)	Girls Mean (SD)
Age (years)	8.01 (0.64)	8.67 (0.72)
Duration (years)	3.55 (1.1)	3.80 (0.7)
Anthropometric measures		
Weight SDS	3.75 (1.94)	3.49 (2.01)
Height SDS	0.25 (3.59)	0.12 (2.12)
BMI SDS	5.25 (2.32)	4.78 (1.53)
Sum of skinfolds SDS	3.36 (1.52)[a]	2.33 (1.36)
Blood pressure (mm Hg)		
Systolic PB (mm Hg)	105.16 (12.54)	106.66 (7.61)
Diastolic PB (mm Hg)	72.96 (11.89)	71.25 (8.50)
Metabolic profile		
Glucose (mg/dL)	95.22 (7.84)	97.0 (9.36)
Insulin (μU/mL)	10.61 (6.98)	10.17 (8.20)
HOMA-IR	2.32 (1.59)	2.45 (1.86)
Total cholesterol (mg/dL)	162.59 (33.14)	168.50 (45.71)
HDL-C (mg/dL)	41.31 (13.27)	42.65 (16.24)
LDL-C (mg/dL)	116.73 (25.8)	122.12 (32.87)
Triglycerides (mg/dL)	82.25 (28.85)	81.75 (40.56)
Ultrasound		
Visceral fat (mm)	65.42 (15.97)[b]	52.70 (17.42)
Subcutaneous fat (mm)	23.76 (1.52)	21.08 (6.84)

[a] *t*-test, [b] Mann-Whitney, *P*<.05 for both.

RESULTS

The anthropometric, clinical and biochemical characteristics of the 60 obese children (28 boys and 32 girls) are shown in **Table 1**. A statistically significant difference between genders was found for the sum of SDS for the skinfold thicknesses and ultrasound visceral fat thickness, with boys presenting higher values. **Table 2** shows comparison of the clinical and biochemical characteristics between the obese boys and girls and their normal weight control groups. Waist circumference, WHR, visceral and subcutaneous fat thickness, levels of systolic and diastolic BP, insulin, HOMA-IR and LDL were significantly higher in obese boys and girls compared to controls. On the other hand, HDL was significantly lower in both obese boys and girls compared to their normal weight children. Total cholesterol showed a trend towards higher levels in obese children.

Table 3 compares clinical and biochemical characteristics between obese children with and without MS. The mean (SD) age of children with MS was 8.43 (1.37) compared to 8.60 (1.64) of children without MS (not statistically significant). Duration of obesity, BMI SDS, sum of skinfold thicknesses SDS, waist circumference, visceral fat thickness, systolic and diastolic BP, HOMA-IR, insulin and triglycerides were significantly higher in children with MS compared to children without MS. However, significantly lower HDL was found in MS children compared to non- MS children. Acanthosis nigricans was detected in 20% of obese children with MS. **Table 4** shows the prevalence of components of MS according to presence of metabolic syndrome. None of the children fulfilled the five criteria of the MS. The prevalence of the components of MS among obese children was as follows: abdominal obesity, 85%; high systolic BP, 8.3%; high diastolic BP, 5%; impaired fasting glucose, 8.3%; hyperinsulinemia, 25%; HOMA-IR values, 28.3%; high total cholesterol, 8.3%; hypertriglyceride-

Table 2. Descriptive clinical and biochemical characteristics of obese and control groups.

Features	Boys		Girls	
	Obese	Normal weight	Obese	Normal weight
Age (years)	8.01 (0.64)	8.353 (0.65)	8.67 (0.72)	8.67 (0.24)
Systolic BP (mm Hg)	105.16 (12.54)[b]	96.61(7.82)	106.66 (7.61)[b]	102.5 (6.12)
Diastolic BP (mm Hg)	72.96 (11.89)[b]	66.61 (7.82)	71.25 (8.50)[b]	67.77 (10.29)
Waist circumference (cm)	87.88 (14.02)[a]	63.89 (11.1)	89.95 (11.73)[a]	57.23 (8.71)
Waist to hip ratio	0.93 (0.05)[a]	0.87 (0.11)	0.90 (0.05)[a]	0.87 (0.04)
Glucose (mg/dL)	95.22 (7.84)	92.18 (8.48)	97.00 (9.36)	93.83 (9.21)
Insulin (μU/mL)	10.61 (6.98)[b]	6.29 (3.79)	10.17 (8.20)[b]	6.94 (5.23)
HOMA-IR	2.32 (1.59)[a]	1.41 (0.85)	2.45 (1.86)[a]	1.61 (1.23)
Total cholesterol (mg/dL)	162.59 (33.14)	155.64 (30.56)	168.50 (45.71)	166.91 (26.55)
HDL-C (mg/dL)	41.31 (13.27)[b]	50.21 (21.22)	42.65 (16.24)b	53.36 (22.28)
LDL-C (mg/dL)	116.73 (25.8)[b]	99.07 (36.38)	122.12 (32.87)[b]	112.02 (31.65)
Triglycerides (mg/dL)	82.25 (28.85)	80.82 (43.18)	81.75 (40.56)	79.82 (30.18)
Ultrasound visceral fat (mm)	65.42 (15.97)[b]	48.21 (13.39)	52.70 (17.42)[b]	45.73 (11.88)
Ultrasound subcutaneous fat (mm)	23.76 (1.52)[b]	13.20 (6.37)	21.08 (6.84)	17.86 (17.17)

Values are mean (standard deviation). [a]*t* test for the differences between obese and normal weight children, *P*<.05. [b]Mann-Whitney for the differences between obese and normal weight children, *P*<.05.

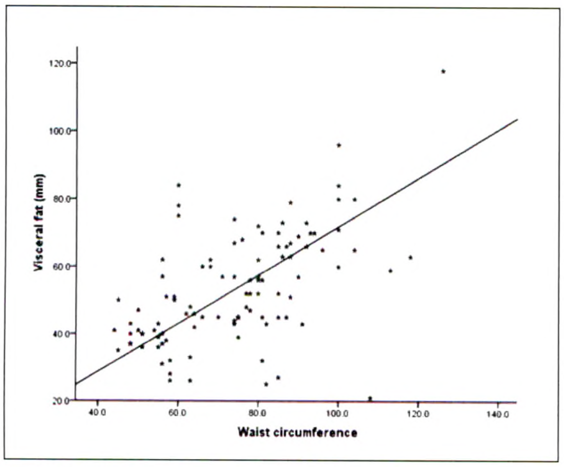

Figure 1. Relationship between visceral fat and waist circumference in obese children.

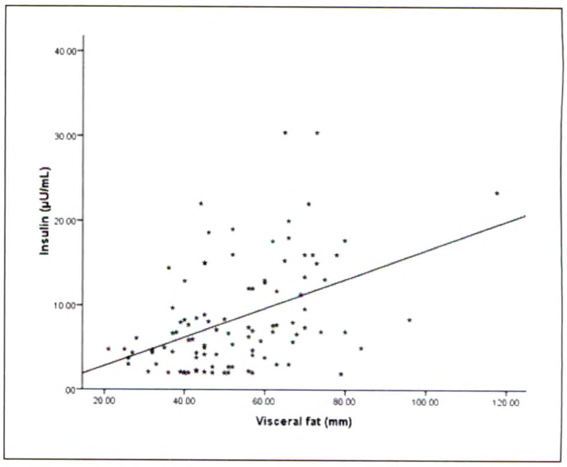

Figure 2. Relationship between fasting serum insulin levels and visceral fat in obese children.

mia, 13.3%; high LDL, 8.3%, and low HDL-C, 20%. High frequency of high diastolic BP, insulin concentration level, HOMA-IR value, triglycerides and low HDL were observed in the obese children with MS compared to children without MS (*P*<.001).

Table 5 shows the ORs of suffering MS according to IR categories. From this table, it is apparent that the odds of developing MS (adjusted for gender and age) increases as a function of IR. Such OR is 5.7 (95% CI 2.34-11.55) times greater when IR is above the 75th percentile (*P*<.001). **Figure 1** shows positive significant relation between waist circumference and visceral

Table 3. Descriptive clinical and biochemical characteristics of the obese children according to the presence or absence of metabolic syndrome.

Parameters	With MS (n=15)	Without MS (n=45)
Age (years)	8.43 (1.37)	8.60 (1.64)
Duration	4.07(1.01)[a]	3.18 (1.07)
Anthropometric Measures		
Weight SDS	4.07 (3.40)	3.78 (2.17)
Height SDS	0.18 (2.41)	0.25 (2.83)
BMI SDS	7.07 (2.22)[a]	3.35 (2.48)
Sum of skinfolds SDS	3.09 (1.46)[a]	2.97 (1.79)
Waist circumference (cm)	96.20 (12.99)[a]	84.03 (12.23)
Waist-to-hip ratio	0.94 (0 .03)	0.91 (0.06)
Blood Pressure		
Systolic (mmHg)	108.66 (14.45)[a]	101.0 (9.92)
Diastolic (mmHg)	76.67 (14.09)[a]	69.78 (10.44)
Metabolic Profile		
Glucose (mg/dL)	91.33 (9.81)	90.04 (8.02)
HOMA-IR	3.97 (1.77)[a]	1.58 (1.03)
Insulin (μU/mL)	17.52 (7.64)[b]	7.32 (4.55)
HDL-C (mg/dL)	37.80 (11.33)[b]	42.68 (16.18)
LDL-C (mg/dL)	124.0 (21.69)	117.31 (32.65)
Triglycerides (mg/dL)	110.33 (37.53)[b]	85.09 (84.31)
Total cholesterol (mg/dL)	168.73 (26.99)	157.82 (42.36)
Ultrasound		
Visceral fat (mm)	70.33 (18.07)[b]	54.59 (15.73)
Subcutaneous fat (mm)	24.93 (8.87)	21.43 (7.94)
Gender (M/F)	8/7	24/21
Acanthosis	3 (20%)	2 (4.4%)

Values are mean (standard deviation) or number (percent).

[a] *t*-test for the differences between absence or presence of MS, *P*<.05; [b] Mann-Whitney for the differences between absence or presence of MS, *P*<.05

Table 4. Prevalence of components of MS according to presence of metabolic syndrome.

Components of MS	Total Obese (n=60)	With MS (n=15)	Without MS (n=45)	*P*
Waist circumference ≥90 pc	85%	100%	80%	.09
Systolic BP ≥90 pc	8.3%	20%	4.4%	.09
Diastolic BP ≥90 pc	5%	20%	4.2%	.04
Glucose ≥100 (mg/dL)	8.3%	20%	4.4%	.09
Insulin ≥15 (μU/mL)	25%	73.3%	8.8%	.0001
HOMA-IR (≥3.4)	28.3%	73.3%	13.3%	.0001
Total cholesterol ≥200 (mg/dL)	8.3%	20%	4.4%	.09
Triglycerides ≥150 (mg/dL)	13.3%	40%	4.4%	.002
LDL- C ≥130 (mg/dL)	8.3%	20%	4.4%	.09
HDL-C <40 (mg/dL)	20%	53.3%	8.8%	.0007

Data are number (%).

Table 5. Risk of suffering from metabolic syndrome according to HOMA-IR percentile values by logistic regression analysis.[a]

HOMA-IR percentile (values)	Significance	OR	95.0% CI for OR	
			Lower	Upper
<25 pc (<2.4)	-	Referent	-	-
25-49.9 pc (2.4-3.3)	0.46	1.2	1.022	2.28
50-74.9 pc (3.4-4.9)	0.003	3.8	1.104	8.86
≥75 pc (≥5)	<0.001	5.7	2.34	11.55

[a] Values obtained through logistic regression analysis, adjusted for gender and age. OR: Odd ratio, Pc: Percentile, CI: Confidence interval

fat thickness in obese children (r=0.56, *P*<.05). **Figure 2** positive significant relations between fasting serum insulin level and visceral fat in obese children (r=0.41, *P*<.05).

DISCUSSION

Global analysis showed a rising trend in childhood overweightness in developing countries in more than one national survey.[20] In 38 countries for which secular data were available, 16 showed a rising trend in obesity prevalence over time, 16 were static, and only 8 showed falling rates in obesity prevalence.[7] Rates of increase seemed most marked in the countries of northern Africa, such as Morocco and Egypt. Generalized obesity in Egypt and its association with certain chronic diseases has been reported in the literature among adults.[21,22] The results of our study demonstrate that MS components, which until recently were associated with adult morbidity, are also found to be highly prevalent among obese children in our community. The present study revealed that the prevalence of MS was 25% in obese children with no sex tendency, 85% presented with abdominal obesity, a criterion of MS. The observed prevalence of MS in our study is higher than in European countries.[8,23,24] In Western countries, the incidence of childhood obesity has more than doubled over the past generation; as a consequence, the prevalence of MS and type 2 diabetes mellitus is rapidly increasing in the pediatric population.[25] A previous study on 4250 adolescents (from 10 to 18 years of age; male subjects comprised 42.5% of participants) from 7 governorates representing Egypt showed that MS was 7.4% with no sex or area of residence predilection and that more than one-third of obese Egyptian adolescents had criteria for MS.[2] The present study is the first Egyptian one on the frequency of MS and associated metabolic complications among obese children aged 7 to 9 years. In studies where the Cook criteria were applied, the prevalence of MS among North American obese adolescents was 27%.[17] In others studies following the III Adult Treatment Panel criteria, the prevalence was 26.1%.[26] However, there is no consensus about the definition of MS in pediatric populations.[23] Until recently, even if the MS was reported in children, several definitions were developed. The International Diabetes Federation (IDF) developed a simple unified definition for children over 10 years of age.[27] Many different MS criteria have been employed in children and adolescents, and the components and cut-offs used to diagnose this syndrome have varied considerably among studies.[17,23] The mean age of the children in this study was approximately 8 years, and as the IDF definition was proposed only for children over 10 years we used the the Cook definition.[17] Changes in growth and development during childhood and adolescence make it difficult to choose a cut-off for risk factors.[28,29] To ascertain the real prevalence of this syndrome among children, agreement is needed on the cut-off points for each of the syndrome components; likewise, categories for pubertal stage and gender need to be established.

Environmental factors, including health-related behaviors or lifestyle changes and economic disadvantage, contribute to some of the race or ethnic disparities in the prevalence of the diseases associated with obesity. In cross-sectional population studies, higher fasting serum insulin levels are directly related to increases in body fatness, particularly in those with central adiposity.[30,31] Obesity is an important factor in the development of hypertension in children.[32,33] In our study, BP measurements were significantly higher in both obese males and females compared to controls. The influence of obesity in Egyptian children may be affected by the specific genetic background of the population. Hispanic individuals have a greater risk of developing diabetes and insulin resistance than other ethnic groups.[34,35] The present study clearly confirms that metabolic components are more common in obese children than in controls. Dyslipidemia is more prevalent in obese children with higher HOMA-IR and LDL and lower HDL than a normal weight group.

There was no significant correlation in the present study between regional fat accumulation and blood pressure in obese children. The study showed a significant positive association between waist circumference and visceral fat as well as between visceral fat and insulin level in obese children (**Figures 1, 2**) in accordance with previous studies indicating that WC provides a simple yet effective measure of truncal obesity.[36,37] WC in obese children was more related to US measurements when compared with that in the control group. No relationship between WHR and ultrasonographic fat thickness measurements was found in either group. These results suggest that WC, but not WHR, might be a useful index to show truncal obesity. In some studies in children and adolescents, there is no correlation between WHR and visceral fat measured by various techniques.[36,38]

Children with MS had significantly different higher levels of BMI SDS, sum of skinfolds thicknesses SDS, waist circumference, visceral fat thickness, systolic and diastolic BP, HOMA-IR, insulin and triglycerides compared to children without MS. However, significantly lower HDL was found in MS children compared to nonMS children. The reason why some obese children developed this syndrome, while others do not is still unknown.[10] This may be due to the presence of other underlying factors, such as IR. Indeed, IR seems to be an important pathophysiologic event contributing to MS, becoming more important than overall adiposity in the development of this syndrome.[4,9,39] In accordance with previous studies, the IR reported in this study was associated with the primary alterations in lipid profile; hyperinsulinism increases free fatty acid release and triglyceride synthesis, which results in hypertriglyceridemia.[40,41] The lipid profile can be considered more atherogenic in MS children, with higher TG, LDL, VLDL and apolipoprotein B, and lower HDL and apolipoprotein AI. Our results show that higher levels of IR are associated with a greater degree of alterations in the components of the MS in obese children. HOMA-IR values above 3.4, which correspond to the 50th percentile of this population, were associated with an increased risk of having MS, compared to the lowest percentile of HOMA-IR value. The most important finding in this study is that insulin resistance and obesity are both strongly associated with MS in children. These findings are supported by the previous results of a multiple regression analysis with the use of insulin resistance and BMI as independent factors and with adjustment for other factors.[35] Consistent with several studies,[7,42,43] in our study, obese children with MS had higher frequencies of central obesity, high insulin, HOMA-IR, triglycerides, diastolic BP levels and low HDL level than nonMS obese children. Although the children in our sample were young, the children with MS already had acanthosis, elevated insulin and increased HOMA-IR. Despite this, fasting glucose levels were normal which reflects the range of abnormalities of glucose homeostasis associated with childhood obesity. Even in the obese, high fasting glycemia is not common in children.[44]

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original article

Chronic recurrent multifocal osteomyelitis: a first report from Saudi Arabia

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BACKGROUND AND OBJECTIVES: Chronic recurrent multifocal osteomyelitis (CRMO) is a rare, systemic, aseptic, inflammatory disorder that involves different sites. Pathogenesis of chronic recurrent multifocal osteomyelitis is currently unknown. To our knowledge, there are no reports of CRMO from Saudi Arabia. We describe the clinical and laboratory features and treatment of a cohort of children with CRMO.

DESIGN AND SETTING: Retrospective, patients referred to pediatric rheumatology clinic at a tertiary care center in Riyadh, Saudi Arabia.

PATIENTS AND METHODS: The diagnosis of CRMO was based on evidence of recurrent osteomyelitis with radiographic evidence of chronic osteomyelitis involving at least two sites in the absence of infectious cause in a child less than 14 years old.

RESULTS: Ten patients (9 female, 1 male) with CRMO; 2 patients presented in infancy. The referral diagnosis was inaccurate in all patients. All of them presented with pain and 8 of them had associated swelling and were found to have multifocal lesions. Imaging studies showed findings consistent with chronic osteomyelitis. Histopathological and microbiological examination confirmed the diagnosis in 9 patients. Cyclic pamidronate infusions induced good improvement in 6 patients.

CONCLUSION: This report indicates that CRMO may be overlooked in our community. Early diagnosis and treatment are required to avoid potential complications.

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare systemic autoinflammatory disorder. It is an osteopathy characterized by multifocal recurrent noninfectious lytic lesions, predominantly in the metaphyses of the long bones.[1,2] The disease is characterized by bone pain and soft tissue swelling with or without fever. The disease has an episodic course with periods of exacerbations and remissions. It might be associated with other inflammatory conditions such as pustulosis palmoplantaris, Sweet syndrome, psoriasis and pyoderma gangrenosum and inflammatory bowel disease.[3-5] Like other autoinflammatory disorders, the etiology is largely unknown; it results from complex interactions between a number of predisposing factors in genetically predisposed individuals. As in other rare disorders, there is no standardized therapy for CRMO patients. The disease has worldwide distribution. To our knowledge, there are no reports of CRMO from Saudi Arabia. In this study, we describe the clinical and laboratory features and treatment of a cohort of children with CRMO seen at King Faisal Specialist Hospital and Research Centre (KFSHRC) in Riyadh, Saudi Arabia.

PATIENTS AND METHODS

Medical records of all children with CRMO seen between 1990 and 2010 at KFSHRC, Riyadh were reviewed. The diagnosis of CRMO was made on the basis of the following criteria: evidence of recurrent clinical signs of osteomyelitis (localized pain, swelling, and impairment of limb motion) with radiographic evidence of chronic osteomyelitis (osteomyelitis with sclerosis) involving at least two sites in the absence of an infectious cause in a child less than 14 years old. All patients were reviewed retrospectively for demographic characteristics, age at disease onset, disease duration, follow-up duration, referral diagnosis, musculoskeletal findings and extra-osseous manifestations that could be seen in association with CRMO, including dermatologic manifestations and other systemic diseases such as synovitis.

Laboratory data including histological and radiological findings as well as the treatment and outcomes were reviewed. Active disease was defined by patient reporting of ongoing or deteriorating musculoskeletal findings, increase in the erythrocyte sedimentation rate (ESR) and/ or C-reactive protein (CRP), and radiological evidence of disease progression. In contrast, improvement was defined by pain and swelling relief and improvement in the inflammatory markers and radiological findings.

RESULTS

Ten children (9 female, 1 male) were diagnosed with CRMO during the study period. The age of onset ranged from 2 to 144 months with mean of 55.5 months; 2 patients had their disease onset before 6 months of age while the age of diagnosis ranged from 5 to 147 months with mean of 87.6 months. There was a mean delay of 18 months (ranged 3-87 months) before referral to our hospital and diagnosis after the first symptoms had appeared. All patients were referred to our clinic with an inaccurate diagnosis. All patients had bony pain, 7 patients had associated low grade fever. The associated bony/soft tissue swelling was seen in 8 patients. All patients had multifocal lesions with relapses. A total of 31 individual bones were affected with an average of 3 bones affected in each patient. The femur was the most affected bone followed by the tibia and clavicle. Two patients had vertebral bone involvement, but no associated compression fractures and one had unilateral sacroilitis at the time of diagnosis. Among the 10 patients, one patient had sternum and another patient had mandible involvement. Five patients had associated arthritis. Only two patients had cutaneous manifestation, one had psoriasis and one had vitiligo.

Three patients had a low total white cell count that ranged from 3.2-4.0×10^9 (5-15×10^9/L) with a normal differential cell count; one also had anemia with a transient positive direct Coombs test and a weakly positive antinuclear antibody with a titer of 1:160 (<1:40). However, the extractable nuclear antigens and complement levels were normal. None of the patients had a low platelet count or abnormal cells in the peripheral smear. Eight patients (80%) had elevated ESR with mean of 73 that ranged from 21-123 mm/h (0-5 mm/h); in contrast, only 3 patients had elevated CRP. Unfortunately, HLA-B27 was not done for the patient with sacroiliac joint involvement. All other laboratory markers were unremarkable.

Table 1 summarizes the demographic features, lesion distribution and treatment. All patients had a plain x-ray and technetium bone scan which confirmed the bony lesions in all patients but one, who had an inconclusive bone scan study. The plain x-ray studies showed

Table 1. summarized the demographic features, lesions distribution and treatment.

Patient	Age at onset (Months)	Age at diagnosis (Months)	Referral diagnosis	Associated symptoms	Location of lesions	Treatment	Outcome
1	60	68	Osteomyelitis/ bone tumor	Bone pain, fever	L femur, L tibia, L navicular	NSAID	Partially improved
2	84	96	Chronic osteomyelitis	Bone pain, swelling, fever	R humerus, R iliac bone	NSAID	Partially improved
3	48	68	Histocytosis	Bone pain, swelling	Both femurs	NSAID, Bisphosphonates	Improved
4	2	5	Chronic osteomyelitis	Bone pain, swelling	R radius, L radius, R tibia, fibula	NSAID, Steroids, MTX	progressive course (lost follow up)
5	26	74	Undiagnosed	Bone pain, fever	R sacroiliac Joint, S1, R clavicle	NSAID, Steroids	Partially improved
6	50	65	Undiagnosed	Bone pain, swelling, fever	Body of sternum, L clavicle, R navicular	NSAID, Steroids Bisphosphonates	Improved
7	78	131	Arthritis of R hip	Bone pain, swelling, fever	Bilateral iliac, R 2nd tarsal, L5	NSAID, Bisphosphonates	Improved
8	3	90	Caffey disease	Bone pains welling, fever	R femur, R tibia, both maxillae, R mandible	NSAID,Steroids Bisphosphonates	Improved
9	144	147	Immunodeficiency	Bone pain, swelling, fever	R femur, L tibia, R clavicle	NSAID,Steroids Bisphosphonates	Improved
10	120	132	Chronic osteomyelitis	Bone pain, swelling	R femur, R clavicle, R 4th rib	NSAID,Steroids Bisphosphonates	Improved

combinations of lytic and sclerotic lesions and periosteal reactions in more than one site. All but one patient had a bone biopsy prior to diagnosis of CRMO to exclude other diagnoses of malignancy or infectious osteomyelitis. Histopathology examination showed a chronic inflammatory reaction with a predominance of granulocytic/lymphocytic infiltrate in 5 patients while 4 patients had fibrosis with minimal chronic reaction. Cultures and special stains of bone biopsy specimens for bacteria, fungi and mycobacteria were negative.

All patients were treated with broad spectrum antibiotics without improvement. None of our patients had spontaneous remission. All of our patients received nonsteroidal anti-inflammatory drugs (NSAID). However, NSAIDs alone were sufficient to achieve remission in only two patients. Systemic corticosteroids were used in eight patients and methotrexate was added in one patient. In six patients with frequent relapses, cyclic pamidronate infusion was used. All treated patients received one-day intravenous pamidronate treatment (1 mg/kg/day, with maximum dose of 60 mg/day) once every 3 months. Pamidronate treatment was well tolerated and induced significant improvement in the clinical symptoms and radiological findings. **Figure 1** shows the effects of pamidronate in one of our patients. None of our patients required treatment with biological agents.

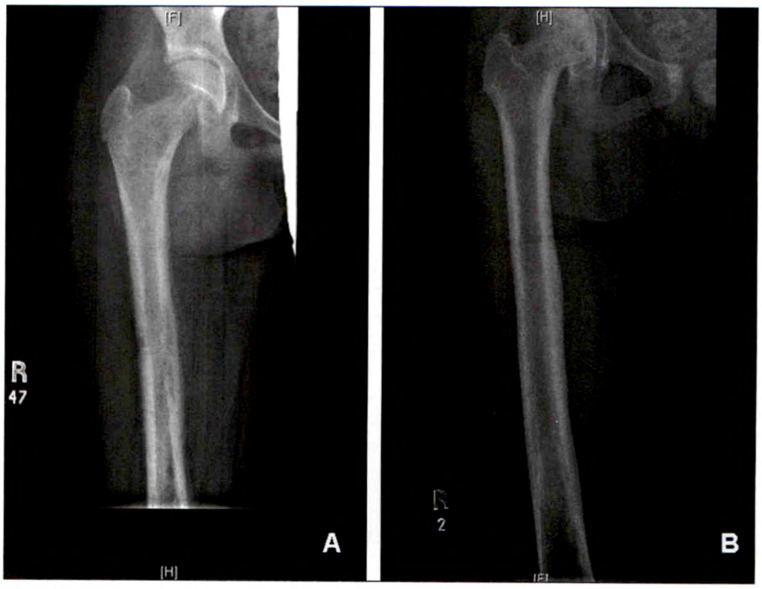

Figure 1. A) Lytic lesions with wide zone of transition involving the neck and shaft of the right femur with interrupted periosteal reaction. B) Improvement of the overall bone density as compared to the previous film. These findings are suggestive of an interval healing process.

DISCUSSION

CRMO is a rare systemic autoinflammatory disorder that primarily affects the skeletal system, though it may also be associated with other autoimmune disorders.[3,4] CRMO usually affects children and was regarded as the pediatric subset of SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome. Recently, however, children with SAPHO syndrome have been described.[2] It is classified as the most severe form of chronic non-bacterial osteomyelitis. The diagnosis is often difficult because the clinical findings and course of disease vary significantly. The diagnosis is usually made by exclusion of other serious entities, namely malignancy and infectious osteomyelitis. The diagnosis is also supported by the presence of multifocal bone lesions and failure of antibiotics and progression of the disease.[2]

The etiopathogenesis of CRMO is unknown. However, several observations suggest the contribution of genetic factors to the etiology of CRMO; mutations in Lpin1-related mouse genes 2 (LPIN2) cause a syndromic form of chronic recurrent multifocal osteomyelitis known as Majeed syndrome.[6-8]

CRMO is described throughout the world. There are several reports from Jordan.[8,9] Unfortunately, no epidemiological data on CRMO from Arab countries exist. To the best of our knowledge this is the first report of CRMO from Saudi Arabia. All our patients had an inaccurate referral diagnosis. All of them were symptomatic with clinical findings involving different bones. Apart from two patients, there was a delay in making the diagnosis. Accordingly, recognizing CRMO might obviate the need for unnecessary investigations or prolonged uses of antibiotics if an infectious etiology is considered.

The clinical presentation of our patients is consistent with previous reports. Bone pain was the most frequent clinical presentation (100%). Most of the patients had bony/soft tissue swelling (80%) and fever (70%). All patients had multifocal lesions. The most affected bone was the femur; only three patients had axial skeletal involvement. Associated autoimmune manifestations were not frequent in our cohort; only psoriasis and vitiligo developed in two patients during the follow-up period. One patient had transient hemolytic anemia with a weakly positive antinuclear antibody; the follow-up assessment did not find any findings supporting the diagnosis of systemic lupus erythematosus.

To date there is no uniformly effective treatment for CRMO. Therapy depends on the disease severity; experts in the field have tried several medications. We used a bisphosphonate (pamidronate) that showed encouraging results in patients with CRMO and recently biological agents such as anti-TNF-α therapy have been considered for severe cases refractory to bisphosphonate.[10,11] We observed significant improvement in the symptoms as well as in the imaging studies in six patients treated with cyclic intravenous pamidronate. We did not use pamidronate for other patients because three patients had been already transferred to the adult service before the availability of pamidronate and the fourth patient was lost to follow up. However, we did not attempt to assess the efficacy of treatment in this cohort because of the study limitations and design. None of our patients needed treatment with biological agents.

CRMO needs to be considered in the differential diagnosis of patients presenting as chronic osteomyelitis whose culture results are negative or when response to antibiotics is not optimal. The outcome of CRMO is usually good, but some patients can have a severe and protracted disease course despite intensive treatments. Few studies have proposed risk factors for persistent disease and probably poor outcome, early onset and number of bony lesions considered to be predictive of poorer outcome.[1,12,13]

All patients in our study were surviving and in stable condition at the time of writing without disability, but one patient was lost follow up. This report indicates that CRMO may be overlooked. Early diagnosis and treatment are required to avoid potential complications.

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Causes of death certification of adults: an exploratory cross-sectional study at a university hospital in Riyadh, Saudi Arabia

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BACKGROUND AND AIMS: Saudi Arabia has no precise data on causes of death. We sought to ascertain the commonest causes of death as stated in death certificates of adults and evaluate the completeness of death certificates at a teaching hospital in Riyadh.

DESIGN AND SETTING: A cross-sectional study carried out at King Khalid University Hospital in Riyadh, Saudi Arabia, during the year 2008.

METHODS: All death certificates that were issued in 2008 were reviewed and data were checked by two reviewers. Causes of death were coded according to specially-designed codes.

RESULTS: The mean (SD) age of death was 63.9 (20.7) years. More than 80% arrived alive at the hospital. Among the 410 certificates, 62.2% had the first reported cause of death being classified as "inappropriate" and this tended to be slightly, but significantly more frequent among women. The first most common appropriately reported cause of death was malignancy of any type (7.3%) followed by ischemic heart diseases (4.9%). Accidents and fractures were more common in the younger age groups and among men.

CONCLUSIONS: This is the first study that documents the possible gaps among healthcare professionals in Saudi Arabia in their understanding of death and its certification based on the clinical assessment of the deceased. The findings needs to be validated by similar studies from other health care sectors. It is clear, however, that proven educational, system-related and legal interventions to improve the accuracy of death certification are strongly needed if the health care priorities are to be properly identified.

When a person dies, the death certificate provides a permanent legal record of the fact that "death" has occurred. At the global level, cardiovascular disease is reported as the most common cause of death among males and females (26.8% and 31.5%, respectively), followed by infections and parasitic diseases (16.8% and 15.7%, respectively) and cancer (13.4% and 11.4%, respectively).[1] Such global results cannot be generalized at regional and country levels without reservations because of the limited, incomplete and uncertain data in many parts of the world. While 44 of 52 countries in Europe had death registration data with coverage of 85% or more, only 2 of 21 East Mediterranean countries had that level of coverage. Saudi Arabia is not one of them.[2]

A simple search strategy of (SaudiTitle/Abstract AND ArabiaTitle/Abstract) AND (causesTitle/Abstract AND deathTitle/Abstract) identified 37 articles in PubMed, none of which was relevant to general causes of death in Saudi Arabia. Searching the grey literature identified two sources of information: the World Health Organization (WHO) press releases and the Saudi Arabian Ministry of Health (MOH) annual reports.

The WHO mortality country fact sheet in 2006 stated that the top causes of death among all age groups in Saudi Arabia were ischemic heart disease (17%) followed by hypertensive heart disease (9%), congenital anomalies (7%), lower respiratory infections (6%), road traffic accidents (6%) and diabetes mellitus (5%). This was based on data released in 2002.[3] In the MOH report for 2009, 31% of the deaths had ill-defined causes, 18% were attributed to injury, poisoning and external causes followed by 17% due to cardiovascular diseases, 9% to perinatal problems, 4.7% to respiratory disorders and 4.6% to neoplasms.[4]

In their assessment of the global status of cause of death data, Mathers et al identified Saudi Arabia as one of the countries that has no recent data (from 1990 or later).[5] Moreover, in the summary estimates for WHO member states for the year 2008, Saudi Arabia was classified in the pink zone which includes the countries where modelling based on nearby countries of the cause of death was used because the country's information on the cause of death were not available.[6] The 2011 noncommunicable disease fact sheet for Saudi Arabia (based on 2008 modelling estimates) suggested that the major causes of death are cardiovascular diseases (42%) and injuries (15%).[7]

In a United States study, death certification completion by physicians was poor with the optimal scoring range of only 23%.[8] In a Canadian study, the death certificate were filled out in an acceptable fashion in 68%.[9] In Australia, major errors were found in 16% of certificates.[10] A study from the UK showed that in the study sample, most (62.4 %) House Officers and (59.3%) of general practitioners were not confident about the cause of death and might modify their statements.[11]

In local or regional context, BinSaeed et al in Saudi Arabia found that the underlying cause of death was misdiagnosed in 80.3% of death reports.[12] In Bahrain, Abulfatih and Hamadeh reported death certificate causes of death were inaccurate in 60% of cases.[13] A study from Lebanon reported that 50% of death certificates did not carry a certifier signature and of those with such a signature, 21.6% lacked documentation of the underlying cause of death.[14]

The aims of the study were to identify the commonly reported causes of death as stated in death certificates and to examine the characteristics and completeness of death certificate data at King Khalid University Hospital (KKUH) which is the main teaching hospital at King Saud University, the oldest university in Saudi Arabia.

METHODS

After getting the approval of the Institutional Review Board of the College of Medicine at King Saud University to conduct the study and waiving the need for the next-of-kin consent, copies of death certificates issued at KKUH in 2008 for those over 12 years of age were retrospectively reviewed. In addition to the personal identification details of the deceased, items to be filled in a traditional death certificate are age, gender, nationality, diagnosis on entry to KKUH (if alive on admission), the causes of deaths and the underlying/contributing factors. No specific codes are used to complete the form. Death certification is usually carried out by two treating physicians without necessarily stating their qualification or position. No special codes for the causes of death are available on the death certificate.

The codes of death created and used in this study were: 1) cerebrovascular disease (stroke), 2) ischemic heart disease (heart attack), 3) heart disease not ischemic in nature (aortic aneurysm, heart failure, etc), 4) lower respiratory diseases (acute or chronic not including malignancies), 5) diseases of the urinary system, not including malignancies, 6) liver diseases not including malignancies, 7) malignancies of any types, 8) septicemia, 9) accidents/fractures, 10) multiple organ failure, 11) inappropriate, 12) not reported, and 13) others. These codes were meant to be in line with the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) Version for 2010.[15] The ICD-10, per se, was not used in this study for coding the causes of death of death because it was difficult to apply in retrospect. Terms like cardiorespiratory arrest, cardiac arrest, respiratory arrest, cardiorespiratory failure, and natural death were considered inappropriate as these terms describe the end stage of life and not the main cause of death. One author (YAA) extracted the data from the copies of death certificates and another author (SEA) checked for accuracy. The study reports the results in terms of rates, means standard deviations (SD) and *P* values. The chi-square test was used because the data were categorical.

RESULTS

Of 427 death certificates reviewed, 346 deceased (81%) arrived alive to the hospital; the remaining 19% arrived dead. Seventeen certificates had no data on the causes of death and therefore were excluded from further analysis. The age in 410 valid certificates ranged from 12 years to 110 years. The mean (SD) age was 63.9 (20.7) years and the most reported age at death was 70 years. Of the deceased, 56.8% were males, 84.8% were Saudi nationals and 81.7% of the people were admitted alive but died later in KKUH. The distribution of the deceased by age group and gender is shown in **Figure 1** and the most common causes of death are shown in **Table 1**. There were 20 death certificates in which the first cause of death was not coded specifically and was classified as "others". "Others" describe terms as acidosis, abdominal bleeding, colonic perforation, diabetes (with no details about the condition), gastrointestinal bleed-

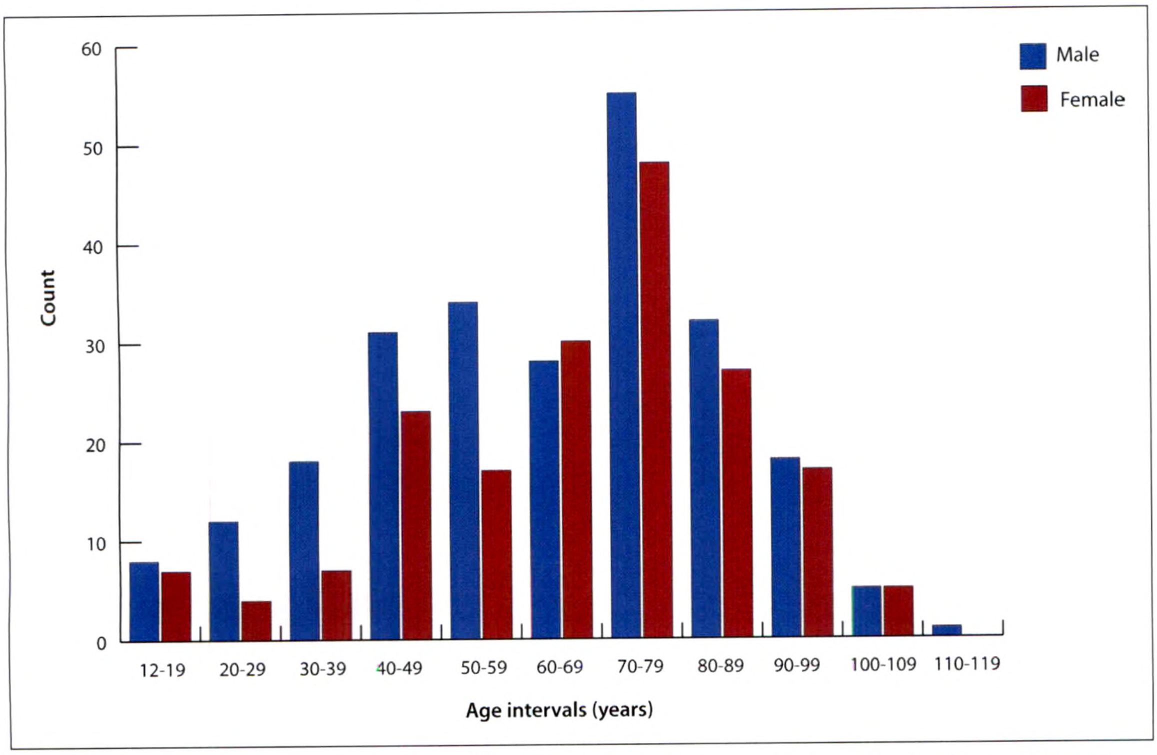

Figure 1.The distribution by age groups and gender of 427 death certificates at King Khalid University hospital, Saudi Arabia (2008).

ing, postoperative surgical procedure, thrombocytopenia, or simply as unknown causes.

When causes of death were assessed in relation to age groups it was found that all the most common causes of death were reported in older groups except accidents/fractures, which were more common causes of deaths in those 45 years of age or younger. In this series of patients, accidents/fractures occurred exclusively among men (**Figure 2**). Apart from that, none of the apparent gender-related differences was statistically significant including the "inappropriate terms" where chi-square=0.73, *P* value=0.4. **Table 2** compares the diagnosis at admission with the cause of death on the death certificate of the 335 patients who arrived alive and had a primary cause on the death certificate. The primary cause of death in the death certificate agreed with the diagnosis on arrival to the hospital in 20.9% of the cases. The agreement ranged from 15.4% in liver diseases (excluding cancers) to 33.8% for malignant neoplasm of any type. Almost 60% of those who arrived alive to the hospital had a primary cause of death that was "inappropriate" and that ranged from 50% of those diagnosed initially with septicemia to 64.7% of those diagnosed to have a disease of the urinary system (excluding cancers).

Table 1. The most common causes of death in a teaching hospital in Saudi Arabia (2008).

	Coded causes of death	No.	%
1	Malignant neoplasm of any types	30	7.3
2	Ischaemic heart disease (heart attacks)	20	4.9
3	Heart disease not ischaemic (aortic aneurysm, heart failure, etc)	20	4.9
4	Lower respiratory diseases acute or chronic	15	3.6
5	Accident(s) /Fracture(s)	15	3.6
6	Septicaemia	11	2.7
7	Cerebrovascular disease (strokes)	8	2.0
8	Multiple organs failure	7	1.7
9	Diseases or urinary system , not including cancers	5	1.2
10	Liver disease not including cancer	4	1.0
11	Inappropriate	255	62.2
12	Other(s) any cause that was not coded	20	4.9
	Total	410	100

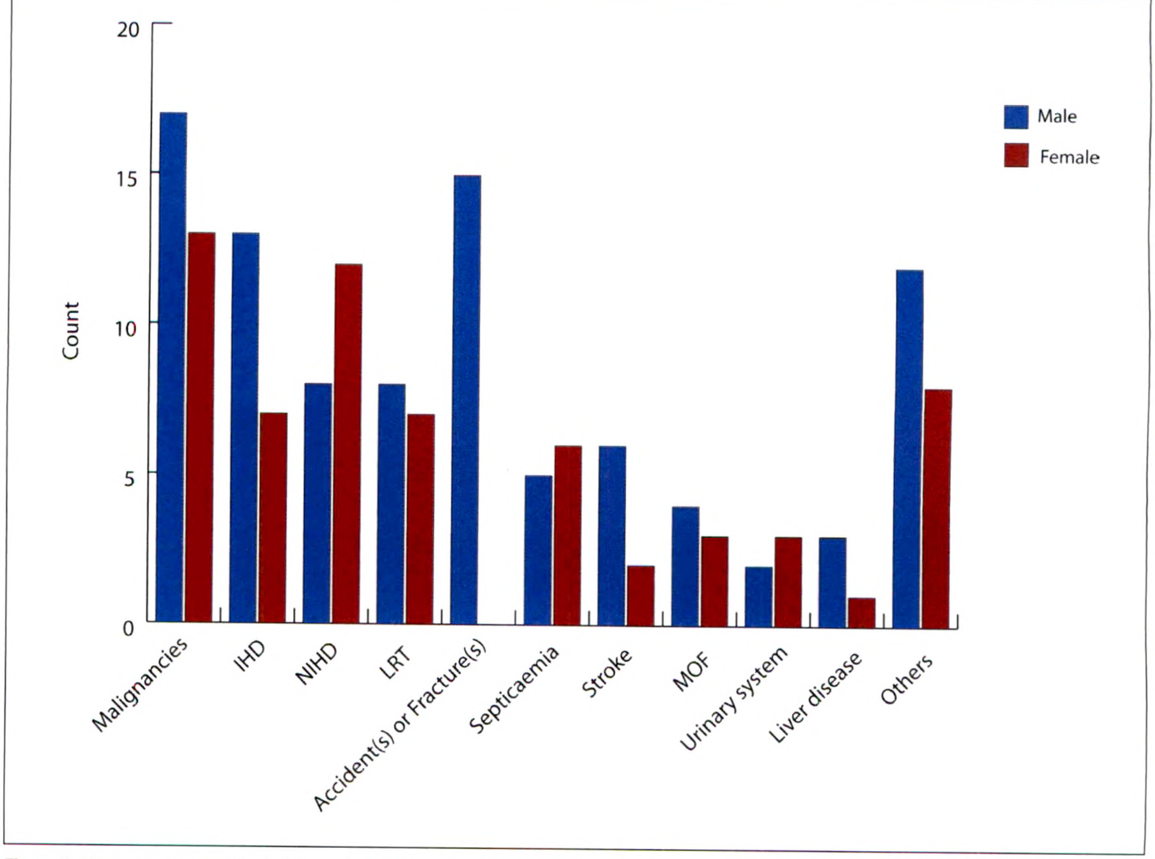

Figure 2. The most commonly and "appropriately" reported causes of death and gender of 155 death certificates at King Khalid University Hospital, Saudi Arabia (2008). Inappropriate causes in 255 death certificates (62.2% of all the deaths in 2008) were excluded. Neoplasm (malignant neoplasm of any types), IHD (Ischemic heart disease (heart attacks), NIHD (heart disease not ischaemic (aortic aneurysm, heart failure, etc), LRT (Lower respiratory diseases acute or chronic), strokes, MOF (multiple organ failure), urinary system (diseases of urinary system not including cancers), liver disease (liver disease not including cancer), others (reported causes that are not coded in the above).

DISCUSSION

Whether from concern, courtesy or curiosity, the common first questions that lay people would ask after learning of the death of another (such as "How did she die?" or "Why did he die?") are essentially probing for the cause of death.[16] Sadly enough, the medical profession is not yet able to provide full answers to such questions.

From the epidemiological point of view, death is one of the most objective outcome measures of the health of any society. It has long been recognized that accuracy in the statistical information on death and its causes will have its impact on preventive activities, on health care planning, on health economics and on identifying the priorities for health care delivery and research.[17-19] In the past decade, it has been realized that even at the level of a primary care centers, analyses of mortality data can provide useful insights for informing health needs assessment.[20] Primary care teams strongly believed that presenting data about mortality in their practice populations can enable them to reflect on their clinical policies.[21]

This study has documented a strongly held belief among health care professionals that the cause of death is not properly identified in the majority of certificates[16,22-24] and cover-up with loose or non-specific terms is often used. These terms describe the mode or mechanism of death (such as cardiopulmonary arrest or natural death) instead of the actual or "true" cause of death.[25] In our study, 62% of the issued death certificates carried such terms to describe the primary cause of death. The classification of "appropriate" causes of death was different from that in WHO and MOH reports. In fact the classification of diagnoses in each of these reports conflicts with the other, which has implications on identifying priorities for health

Table 2. The agreement of the diagnosis at admission with the primary cause of death at King Khalid University Hospital, Saudi Arabia (2008).

Diagnosis at admission	Primary cause of death at the death certificate						
	Same cause		Other cause(s)		"Inappropriate"		Total
	No.	%	No.	%	No.	%	No.
Malignant neoplasm of any type	23	33.8	10	14.7	35	51.5	68
Lower respiratory diseases acute or chronic	10	23.3	10	23.3	23	53.4	43
Ischaemic heart disease (heart attacks)	12	31.6	3	7.9	23	60.5	38
Heart disease not ischaemic (aortic aneurysm, heart failure, etc)	5	22.7	4	18.2	13	59.1	22
Cerebrovascular disease (stroke)	5	26.3	2	10.5	12	63.2	19
Diseases of urinary system, not including cancers	0	-	6	35.3	11	64.7	17
Accident(s) /fracture(s)	5	29.4	2	11.8	10	58.8	17
Septicemia	3	18.7	5	31.3	8	50.0	16
Liver disease, not including cancers	2	15.4	4	30.8	7	53.8	13
Not reported[a]	0	-	17	39.5	26	60.5	43
Others	5	12.8	6	15.4	28	71.8	39
Total	70	20.9	69	20.6	196	58.5	335

[a] Death certificates in which the primary cause of death is not reported were excluded from the analysis.

care delivery, research, planning and funding.

This state of affairs in various countries in the world has been attributed to a number of factors relating to the variable quality of undergraduate and postgraduate training.[26] There is evidence, however, to support that accuracy in completing death certificates does not improve if the certifier is a senior doctor and this would provide the need for a more effective postgraduate medical education.[11] The discrepancies between premortem and postmortem diagnoses were influenced by the type and size of hospital, the age and sex of the patient, the disease responsible for the patient's death[27] and the legislation governing death certification.[26] Qualitative research has identified clinical uncertainty on the part of the certifiers to contribute to the difficulty completing death certificates with certainty.[28]

Diverse efforts have been made to increase awareness and improve the training of practicing physicians on how to identify the cause of death and complete the death certificate, thereby reducing the inaccuracy in death certification. These interventions have included published material,[29] training packages and workshops,[26,30] introducing death certification in medical examinations and in continuing professional development activities.[26,31]

Some studies have suggested that such educational efforts might be successful[32-35] especially if the intervention is interactive.[36] Other reports had conflicting results. Despite the introduction of formal training in the undergraduate curriculum at the University of Leicester in the UK, only 55% of the death certificates were completed to a minimally accepted standard.[37] A recent systematic review restored confidence in the impact of cause-of-death education.[38] The review emphasized that education for certifiers of deaths should be recognised as a fundamental requirement for high quality mortality statistics. It stressed on the interactive format and on the importance of giving feedback regarding the quality of death certification to individual certifiers, training certifiers using the standardised curriculum from the World Health Organization-Family of International Classifications Network (WHO-FIC) has the potential to improve the consistency in death certification practices and subsequently the comparability of epidemiological data.

Other methods were suggested for reducing errors in completing the death certificates such as the need for two certifiers and the need to cross check with relatives (proxy reports).[39] The latter was suggested as a method of improving the accuracy of mortality data and reducing "ill-defined" causes of death.[40,41] A large cohort study suggested that adjudication-based determination of the cause of death might be the "gold standard" especially for cardiovascular diseases and ill-defined causes of death.[42] The adjudication committee used all available data about the cause of death (hospital records, medical data obtained from family physicians or specialists, and proxy interviews). The amount of time and resources, however, required to assemble materials and clinicians for adjudication on a regular basis may be beyond the scope of clinical practice. In reference to adjudication, a recent study has shown that proxy reports (obtained by interviewing the next of kin, family member, or close friend) had similar or higher specificity and higher sensitivity (sensitivity=50%-89%) than death certificates (sensitivity=31%-81%) and was suggested as a better strategy for determining cause of death than mere reliance on death certificates.[43]

Should autopsy be revived in order to get accurate figures? Various studies have suggested that relying on clinical data in determining the cause of death can be seriously misleading and autopsy is still a very important procedure that has a vital role to play.[44-48] In 2005, a systematic review carried out to assess the discrepancy between clinical and autopsy diagnosis showed that a third of death certificates are likely to be incorrect and that half of autopsies identified causes of death that were not thought of.[49] Interestingly, the cases which give rise to discrepancies cannot be identified prior to autopsy.

Skeptics might argue that retrospective analysis of deaths reported to coroners in Australia between 2000 and 2007 showed that coronial investigations transformed basic understanding of cause of death in only a small minority of cases.[50] It should be borne in mind, however, that only selected "reportable" cases (e.g. suspected criminal cases) are referred to the coroner.[51] In other words, one cannot assume that this would be the case for the deaths that were not referred to the coroner.

National surveys have shown a high prevalence of cardiovascular risk factors among adults, namely, overweight and obesity (60%-72%),[52,53] hypercholesterolemia (22%-54%)[54,55] and hypertriglyceridemia (40%),[55] hypertension (26.1%)[56] diabetes mellitus (23.7%)[57] and metabolic syndrome (39.3%).[58] Moreover, a decade-long epidemiological follow-up study showed that the prevalence of these major chronic, non-communicable diseases is on the increase.[59] Nevertheless, cardiovascular events did not appear on the list of major killers. Although studies from different parts of the world identified cardiovascular events[1,60] as the leading causes of death, a large-scale study has suggested that coronary heart disease may be overrepresented as cause of death on death certificates.[61] National mortality statistics, which are based on death certificate data, may overestimate the frequency of coronary heart disease by 7.9% to 24.3% overall and by as much as two-fold in older persons. Discrepancies in initial death certificate diagnoses in sudden unexpected out-of-hospital deaths were demonstrated.[62]

Malignancy was the most common appropriately-identified cause of death in our study. This finding is consistent with two other studies (from Taiwan[60] and Saudi Arabia[12]) and was thought to reflect the ease of identifying it as a cause of death. Nevertheless, it has been nicely demonstrated by Becker et al, in his review of the leading causes of death, that when all cancer categories are grouped together they became the leading cause of death, accounting for 31% of all defined deaths among males and 23% among females.[63] When cancer categories were split they appeared in 4 of the top 10 causes of death in men and 3 in women. The paper proposed that this would be more informative and useful to policy makers.

This was an exploratory study; its findings need to be validated by studies for other health care sectors. It suggests, however, that in its current situation, the only use of the death certificate is to permit burial and legal procedures to be conducted. This is a major clinical and research gap that has to be addressed soon. If death certification is to have an impact on the health care system in this country, then massive and orchestrated educational and legislative efforts have to be exerted without delay.

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Wilson disease in 71 patients followed for over two decades in a tertiary center in Saudi Arabia: a retrospective review

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BACKGROUND AND OBJECTIVES: Wilson disease (WD) is a rare autosomal recessive disease. Our objective was to describe the diverse patterns, therapies, and outcomes of this disease.

DESIGN AND SETTING: A retrospective study over two decades on WD patients in a tertiary care center in Saudi Arabia.

PATIENTS AND METHODS: Clinical and laboratory findings of 71 patients with WD were retrieved from their charts, referral notes and our hospital electronic records and were analyzed.

RESULTS: The mean age and standard deviation was 16.8 (10.7) years and 56.5% were males. The main manifestations of WD were hepatic, neurological, and mixed in 39 (54.9%), 12 (16.9%), and 20 (28.2%) patients, respectively, and 11 (15.5%) were asymptomatic cases detected by family screening. A family history of WD was positive in 41 (57.7%) patients, and consanguinity of parents was found in 26 (36.6%) patients. The mean (SD) follow-up period was 92.2 (72.9) (range, 1-320) months. Ten (14.1%) patients died during follow up, while 45 (63.4%) and 16 (22.5%) were still on or lost from follow-up, respectively. The mean (SD) age at the end of follow-up was 25.3 (12) (range, 4-62) years. Hepatoma was discovered in 5 (7.0%) patients. Penicillamine therapy was used by 58 (81.7%) patients, while zinc and trientine were given to 32 (45.1%) and 11 (15.5%) patients, respectively. Sixteen (22.5%) patients underwent liver transplantation and one died (1.4%) on the waiting list. The liver condition remained stable or improved in 35 (49.3%), and the neurological status showed improvement in 11 (34.4%) of the 32 patients who had neurological involvement.

CONCLUSIONS: This is the biggest cohort to be reported from the Middle East. WD presentation and outcome of WD are very diverse, and its diagnosis still depends on clinical, laboratory, and radiological evidence of abnormal copper metabolism. WD should be considered in patients of any age with obscure hepatic and/or neurological abnormalities.

Wilson disease (WD) or hepato-lenticular degeneration is a rare autosomal recessive inborn error of copper metabolism that results from mutations of the *ATP7b* gene on chromosome 13.[1] The *ATP7b* gene product, a P-type ATPase transporter, is responsible for incorporation of copper with apoceruloplasmin and its excretion into bile. Faulty P-type ATPase transporter leads to accumulation of free copper within hepatocytes, its slow release into the blood stream, and its accumulation in extra-hepatic tissues mainly the liver, brain, cornea, skin, joints, and kidneys.[2]

WD may present at any age and was described in every region of the world. Its incidence was estimated at 1 in 30 000 in countries like the United States, Germany, and Japan.[3] However, WD incidence is more common (1 in 3 000 to 10 000) in communities where consanguineous marriages are prevalent such as the Druze, Yemenite, Iranian Jews, and Palestinians.[4] Confirming the diagnosis of WD is usually straightforward late in the course of the disease if both the major clinical and laboratory features are present, namely, typical hepatic and/or neurological findings, Kayser-Fleischer (KF) rings, low serum levels of ceruloplasmin, and increased urinary copper excretion. However, KF rings are often absent in patients who present with liver disease alone. In addition, ceruloplasmin levels may be normal,[5] or even low together with high urinary copper excretion in patients with fulminant hepatic failure secondary to WD.[6] Moreover, asymptomatic siblings of patients with WD, in whom the diagnosis needs to be confirmed or ruled out, may also present with diagnostic uncertainties.[7]

A review revealed only a few studies, of small sample size, on WD in Saudi Arabia,[8-10] where consanguineous marriages exceed 50%.[11] Little is known about the long-term follow-up outcomes of patients with WD in our geographic locality especially with current advances in the diagnosis and management of liver disease including liver transplantation. Therefore, this study presents the experience of a tertiary care center in Saudi Arabia, with 71 patients with WD for over two decades ito illustrate the pattern of disease presentation, diagnosis, therapies, and outcomes.

PATIENTS AND METHODS

The medical records of 71 consecutive patients diagnosed as WD at a tertiary care center in Saudi Arabia between January 1987 and June 2008 were retrospectively reviewed. The center is a major tertiary care center in the central region of Saudi Arabia that receives referrals of patients with neurological and hepatic disorders of unknown etiology for advanced care. Liver transplantation began at this institution in 1996 for some time, and then restarted again in 2001.[12]

The patients' files were studied for various clinical, laboratory, and radiological features at initial presentation and during follow-up. Data pertaining to disease course, medications used, need for transplantation, response to treatment, and complications such as development of hepatocellular carcinoma (HCC) as well as survival were obtained. Institutional approval of the study, and informed written consent for liver biopsy was obtained from patients or their parents. All patients were cared for by one of the authors at a time period of their follow-up.

The diagnostic criteria of WD included at least two of the following: 1) evidence of liver disease and/or neuropsychiatric illness, 2) presence of Kayser-Fleischer (KF) rings by slit lamp examination, 3) low serum ceruloplasmin level <200 mg/L, and 4) elevated pre-treatment 24-hour urinary copper excretion >100 µg/24-hour.[2] The 24-hour urine excretion after challenge by D-penicillamine was performed when required.

Symptomatic patients with WD were classified as neurologic, hepatic or mixed depending on their clinical presentation, magnetic resonance imaging of the brain, liver imaging (ultrasound and/or computed tomography scan) and liver enzymes. The patients were considered to have a neurologic presentation if they had tremor, dysarthria, gait disturbance, or ataxia in addition to the dystonic, Parkinsonian syndromes, and psychiatric symptoms such as anxiety, depression, behavioral disturbances, and cognitive impairment. Patients who were diagnosed with WD as part of their investigation of abnormal liver enzyme were considered to have a hepatic presentation even if they were symptomatic. For mixed-type patients, the neurologic symptoms were apparent with liver involvement. In patients without KF rings or those with normal serum ceruloplasmin, confirmation of the diagnosis of WD was based mainly on: 1) high hepatic copper content (>250 µg/g dry weight of liver),[2] 2) exclusion of other causes of chronic liver disease, 3) magnetic resonance findings in the basal ganglia compatible with WD, and 4) clinical and biochemical response to medical therapy. Liver function tests and other routine laboratory data were performed using standard methods. Serum ceruloplasmin was measured by immunoprecipitation, or oxidase activity. Liver copper concentration in dried liver tissue was measured by flame atomic absorption spectroscopy in a center in the United States.

Data were collected in a preformatted data collection form before being transferred to a Microsoft Excel Sheet, and underwent descriptive and analytical statistics using SPSS; version 15 (IBM Corp, Armonk, New York, United States). Data are presented as means (SD) or number (percentage) as appropriate. The means of continuous variables were compared using the t tests, non-parametric tests (Wilcoxon and Mann Whitney), or one-way analysis of variance (ANOVA) with post-hoc test (Tukey) as appropriate. A Kaplan-Meier curve with the log rank test were used to test cumulative survival. A *P* value of <.05 was considered statistically significant.

RESULTS

The epidemiological features of the 71 patients with WD are shown in **Table 1**. Most were Saudis (93%). The other 5 patients were Yemenis (n=3) and Syrians (n=2). Regional distribution and the occupation at the time of presentation of the 71 cases are shown in **Figures 1 and 2**. As expected, most (n=26, 36.6%) were from the central region of Saudi Arabia. A positive family history of WD was found for in 41 (57.7%) patients, and consanguinity of parents was reported in 26 (36.6%) patients. Definite nonconsanguinity was reported by 29 (40.8%) patients, and in the remaining 16 (22.5%), parental consanguinity was not documented

Table 1. Patient epidemiological characteristics (n=71).

Variable	Results
Age at onset (years)	
Mean (SD)	16.8 (10.7)
Median (range)	15 (2-49)
Age at end of follow up	
Mean (SD)	25.3 (12)
Median (range)	23 (4-62)
Male gender	40 (56.3)
Body mass index	
Mean (SD)	20.9 (6.1)
Median (range)	19 (12-42) kg/m
Saudi nationals	66 (93)
Disease pattern, n (%)	
Hepatic	39 (54.9)
Hepatic Hepatic and Neurological	20 (28.2)
Neurological	12 (16.9)
Family history	41 (57.7)
Consanguinity	26 (36.6)

Data expressed as number (percent) Or mean (standard deviation) unless otherwise indicated.

Table 2. Frequency of symptoms and signs at the time of presentation.

Symptom	Frequency	Sign	Frequency
Yellow sclera	31 (43.7)	Jaundice	29 (40.8)
Fatigue	12 (16.9)	Lower limb edema	14 (19.7)
Anorexia	4 (5.6)	Spider nevai	0 (0.0)
Abdominal distension	19 (26.8)	Palmar erythema	1 (1.4)
Tremors	13 (18.3)	Ascites	21 (29.6)
Akinesia/ dyskinesia	7 (9.9)	Hepatomegaly	18 (25.4)
Dystonia	22 (31.0)	Splenomegaly	25 (35.2)
Confusion	6 (8.5)	Abnormal movements	13 (18.3)
Psychiatric	14 (19.7)	Hepatic encephalopathy	4 (5.6)

Only those reported in >5% of cases are presented. Data expressed as number (percent)

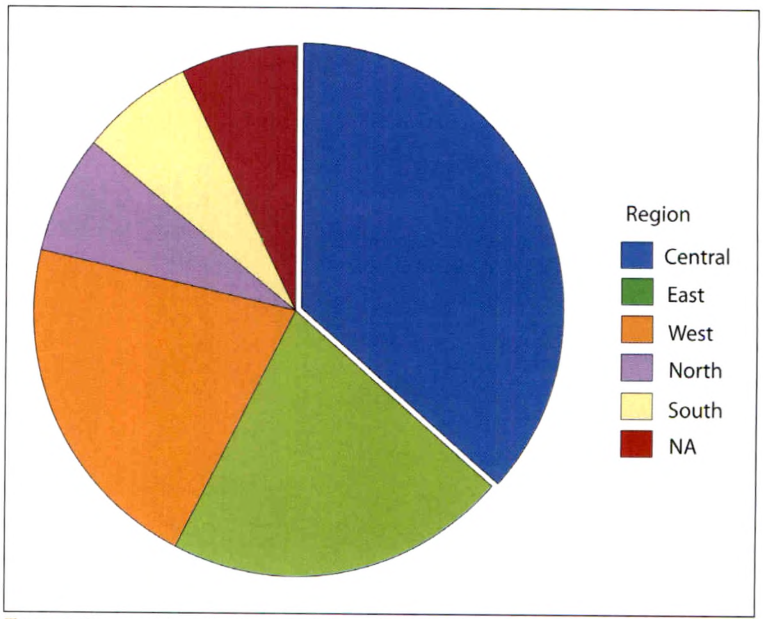

Figure 1. Geographical distribution of the cohort showing number of patients from each region (n=71).

in the medical files (**Table 1**).

Symptomatic disease at the time of presentation was the case in 60 (84.5%) patients, while 11 (15.5%) were asymptomatic subjects detected by family screening. The main manifestations of WD were hepatic, neurological, and mixed in 39 (54.9%), 12 (16.9%), and 20 (28.2%) patients respectively. Clinical findings at the time of presentation are shown in **Table 2**. The clinical, laboratory and pathological findings of the patients presented with hepatic WD and hepatic with neurological affection (n=59; 83.1%) are described in **Table 3**.

KF rings were absent, questionable, and present in 32(45.1%), 3(4.2%), and 36(50.7%) patients, respectively. KF rings were detected at a significantly higher rate in patients who had neurological and mixed pictures; 9/12 (75.0%) and 13/20 (65.0%), respectively, compared to those with hepatic disease alone; 11/39 (28.2%), *P*<.01 for both (**Figure 3**). Liver biopsy in 37 patients found fibrosis stage from stage 2 to 4 (significant fibrosis) in 32 (86.5%) biopsies. Median copper dry weight in the liver biopsy was 298 μg. An abnormal level of dry copper in the liver tissue was seen in 20 (90.9%) of 22 biopsy specimen analyzed for dry copper.

Table 4 shows data on follow up, medical therapy and mortality. Hepatoma was discovered in 5 (7%) patients. Only 45 (63.4%) patients were still on regular follow-up, and 16 (22.5%) were lost from follow-up in our institution, 8 of whom had hepatic disease, 4 had neurological, and 4 had a mixed picture at presentation. These cases were residents of the Central (n=3), Eastern (n=5), Western (n=3), Northern (n=1), and

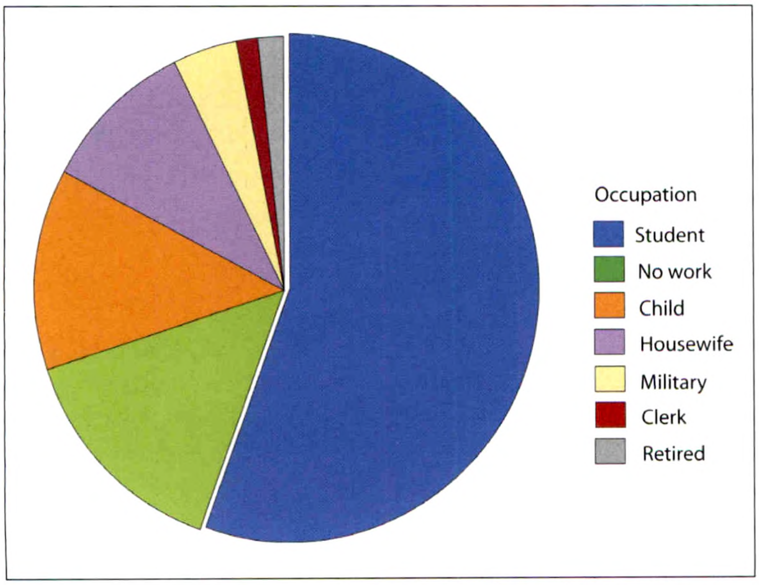

Figure 2. Occupation of the cohort at the time of diagnosis number of patients in each category (n=71).

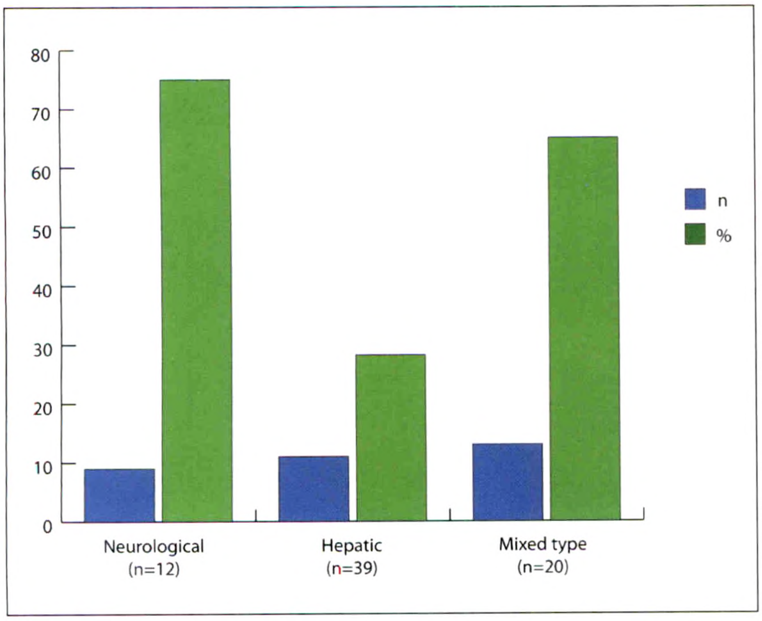

Figure 3. Distribution of Kayser-Fleischer rings finding by slit-lamp examination per disease pattern. * P<.01 compared to the hepatic type.

Southern (n=2) regions, and the remaining 2 cases were non-Saudis.

D-penicillamine therapy was the most commonly used medical therapy. Sixteen (22.5%) patients underwent liver transplantation; 15 (93.8%) were still alive in a good condition at the last follow up. The liver remained stable or improved in 35 (59.3%) of the 59 pa-

Table 3. Characteristics of patients with hepatic and hepatic with neurological Wilson disease (n=59).

Variable	Result
Gender	
Male	32 (54.2)
Female	27 (45.8)
Presentation	
Screening	10 (17.5)
FHF	4 (6.8)
Chronic liver disease	45 (75.7)
Anti-nuclear antibody (n=44)	
Positive	15 (34.1)
Anti-smooth muscle antibody (n=37)	
Positive	23 (62.2)
Liver kidney microsomal antibody (n=22)	
Positive	1 (4.5)
Antimitochondrial antibody (n=28)	
Positive	0 (0.0)
Hepatitis B surface antigen (n=55)	
Positive	2 (3.6)
Hepatitis C antibody (n=55)	
Positive	0 (0.0)
A-$_1$ **antitrypsin (n=22)**	
Deficient	0 (0.0)
Liver Biopsy (n=37)	
Fibrosis stage 2-4	32 (86.5)
Copper quantitation	22 (59.5)
Level of liver copper	20 (90.9)[a]
Liver transplantation, n(%)	16 (27.1)
Mortality	
Yes	10 (16.9)
No	45 (63.4)
Lost-to follow up	16 (22.5)
Brain magnetic resonance imaging (n=34)	
Abnormal	24 (70.6)

[a] 90.9% of those whom liver copper was quantifies.

Data expressed as number (percent)

Table 4. Follow up, therapy, mortality of all patients (n=71).

Variable	Result
Follow up (months)	
Mean (SD)	92.2 (72.9)
Median (range)	96 (1-320)
Medical therapy[a]	
Penicillamine	58 (81.7)
Trientin	11 (15.5)
Zinc	32 (45.1)
Liver transplantation	16 (22.5)
Hepatoma	5 (7)
Mortality (still alive), n(%)	45 (63.4)
Died during follow up	10 (14.1)

[a] Some patients were on more than one drug. Data expressed as number (percent). Or mean (standard deviation) unless otherwise indicated.

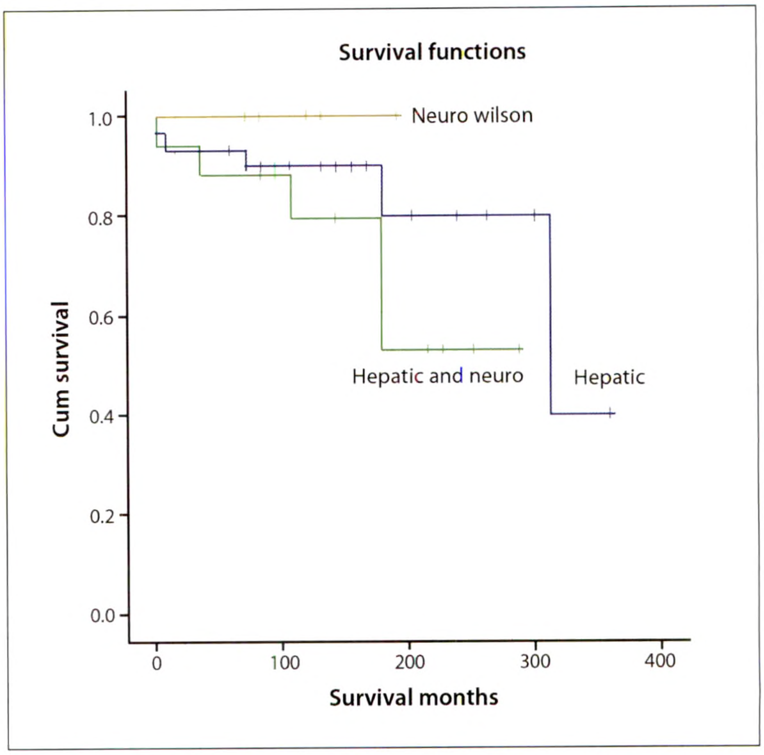

Figure 4. Kaplen-Meier plot of survival analysis of 55 WD patients with hepatic, hepatic with neurological and neurological disease pattern.

tients with hepatic involvement, while neurological disease showed improvement only in 11 (34.4%) of the 32 patients who had neurological involvement (P<.001).

Ten (14.1%) patients died after a median follow- up period of 64 (range, 1-229) months. The main causes of death were Castleman disease (n=1), hepatoma (n=2), post-transplant complications (n=1), and liver failure in 7 cases. Liver failure was associated with septicemia in 1, brain abscess and subarachnoid hemorrhage in 1, and cardiopulmonary complications in 2 cases. Seven of the deceased cases had hepatic disease and 3 had a mixed hepatic and neurological picture. All patients died pre-transplant apart from one who died 6 months post-liver transplant. Prognosis and mortality of 55 patients (excluded 16 cases who were lost to follow up) is shown as a Kaplen-Meier graph in **Figure 4**. None of the patients with pure neurological WD died; 5 patients each from hepatic and mixed (hepatic with neuro logical WD) died during follow up. Cumulative on-treatment survival of the whole cohort at 5, 10, and 20 years was 92.1%, 86.5%, and 57.0% respectively.

DISCUSSION

To our knowledge, this is the biggest cohort of patients with WD reported from the Middle East, and the second worldwide after the German study that describes 163 patients.[13] The second biggest cohort from the Middle East was 56 cases reported from the National Guard Hospital (NGH), another tertiary care centre in Riyadh, Saudi Arabia.[11] This necessitates the establishment of a Saudi National Registry of metabolic diseases, including WD, to be able to obtain more accurate nationwide epidemiological, genetic, and disease-related data.

When added to the cases reported by the NGH in our city, our data has shown that WD is a rather common disease in Saudi Arabia. This is probably related to the high rate of consanguineous marriages among the Saudi population.[13,14] Indeed, the rate of consanguineous marriages in the present series was 36.6% (26/71), which is higher than that in the general Saudi population, despite the fact that consanguinity was clearly documented in the files of only 55 patients.

WD presentation and outcomes are very diverse. Diagnosis is easily made once patients present with low serum ceruloplasmin, KF rings with evidence of liver disease, with or without neuropsychiatric illness. The clinical presentation in our patients was similar to that described in both Saudi patients and in other ethnic groups[11,15-17] and confirms the variable pattern of this disease, and the difficulty in its diagnosis especially at its earlier stages and in patients with atypical presentation.[18]

Similar to any autosomal recessive disorder, it is important to screen family members and siblings of cases with WD not only for early detection that helps in better long-term outcome, but also to prevent or avoid marriage to other undetected cases or carriers in the same or other families. In our cohort, 41 (57.7%) patients had a positive family history of WD, and 11 (15.5%) of our cases were asymptomatic and initially diagnosed by screening. Many of those family members who had WD were either not alive or on follow up at other hospitals.

Our patients did not undergo haplotype analysis to identify any specific mutations that may help in establishing the diagnosis of WD. If available such testing might have been helpful, particularly in determining the disease status in patients who were asymptomatic siblings of index cases and in those who did not have KF rings.[5,19] It is possible that without haplotype analysis, clinicians may still miss asymptomatic WD cases with normal laboratory findings. We do not believe, however, that the risk of routine liver biopsy of siblings is justified if there is no clinical or biochemical evidence of WD. A recent genetic analysis in 56 Saudi patients with WD showed disease causing mutations in three exons (exons 8, 19 and 21) of the ATP7B gene in 28 patients (50%). Such mutations were not detected in 60 control Saudi subjects.[11] Interestingly, mutations in exons 21 (18 cases) and 19 (one case) were reported to be unique for Saudis. These data need to be confirmed by another larger study.

The results of medical therapy for patients who presented in fulminant hepatic failure was rather disappointing as none of our patients with FHF survived while liver transplantation was being awaited. This (100%) mortality rate of patients with FHF in WD warrants an early consideration of liver transplantation and early referral to a transplant center. Sepsis was a leading cause of mortality in all patients.

HCC is a rare complication of WD, published mainly as case reports.[20-22] This lead to the impression that copper and its receptors has a protective role against hepatic carcinogenesis.[23] However, Long-Evans cinnamon (LEC) rats with partial deletion of the copper transporting ATPase gene homologous to the WD gene were found to develop HCC despite the presence of excess copper in their livers.[24] Moreover, copper-chelating agents were found to inhibit the development of liver tumors in the same rat model.[25] The incidence of HCC in patients with WD was attributed to the shortened life expectancy of untreated cases.[26] The development of HCC in 5 (7%) of our cohort suggests that this complication is not uncommon in patients with WD. It was also argued that the HCC may develop in WD patients secondary to associated hepatitis B or C virus (HBV, HCV) infection. However, none of our patients had positive HCV and only 2 were positive for HBV; none of them developed HCC.

Patients with chronic or fulminant liver failure without urgent transplantation have a dismal prognosis. Many recent reports have demonstrated the beneficial role of liver transplantation in patients with predominantly hepatic WD.[27-30] In our cohort, 16 patients underwent liver transplantation, and 15 (93.8%) of them were still alive and on regular follow up, a better outcome compared to medical treatment in one aspect, and in another aspect when compared to transplantation for other chronic liver disease. On-treatment survival of patients with WD has improved. Only 10 patients died in our cohort within 20 years from their initial diagnosis. When including patients lost to follow up (n=16), a cumulative 20-year survival of around 60% can be achieved.

The retrospective nature of any study is an inherent limitation. However, this is not the case in rare metabolic diseases such as WD. Obviously, prospective observational or interventional studies in WD are not feasible unless a worldwide study involving numerous high referral centers is organized. Also, our study still provides more information about disease presentation and outcomes in our locality, and provides the base for future genetic studies.

In conclusion, the diagnosis of WD still depends on clinical, laboratory, and radiological evidence of abnormal copper metabolism with no single test sufficient to make the diagnosis. WD should be considered in patients of any age with obscure hepatic and/or neurological abnormalities. Both a high index of suspicion and family screening are essential for early diagnosis and hence early effective therapy. Long-term treatment of patients with D-penicillamine/trientine along with dietary copper restriction is effective in resolving clinical and biochemical markers of the disease and improves prognosis and possibly survival. Patients who meet current criteria for liver transplantation should be transplanted especially if they present as fulminant liver failure, and if they deteriorate while on medical treatment. Further study on the genetic mutations that occurred in the patients who are still on follow-up as well as the impact of consanguinity is warranted. Moreover, a nationwide registry for metabolic liver disease including WD needs to be established.

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original article

Evaluation of internet use for health information by parents of asthmatic children attending pediatric clinics in Riyadh, Saudi Arabia

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BACKGROUND AND OBJECTIVES: Internet use by patients raises awareness about their conditions, while its use by physicians assists their ability to make evidence-based decisions. This study aimed at assessing the extent, sources and effects of Internet use by parents of asthmatic children in Riyadh, Saudi Arabia.

DESIGN AND SETTING: A cross-sectional design to collect data from two pediatric pulmonology clinics (public, private) for asthma management in Riyadh, Saudi Arabia, during the period of January to May 2011.

SUBJECTS AND METHODS: A specially designed tool was used to collect data from a random sample of 500 parents of asthmatic children. This tool included questions on demographic data (parents, child) and internet use (sources, frequency, purposes).

RESULTS: Most children (77%) in our study sample were diagnosed with asthma before their third birthday, by a treating physician (78%). Among Internet user parents (n=400), 53% used it for 10 to <30 minutes or <10 minutes (22%). Reported reasons for internet use were reassurance, clarification, online consulting, and new management schemes. Reported limitations for Internet use for managing asthma included the nonavailability of Arabic information and highly technical information. Parents suggested the need for the availability of the following online services: consulting/chatting with treating physician, receiving updates on asthma, booking appointments, and being directed to specific websites on asthma. Multivariate analysis showed that the most important predictors for internet use were: "higher mother education" (OR=7.02), followed by "higher father education" (OR=3.04) and "non-health related mother occupation" (OR=2.6).

CONCLUSION: The application of the findings of this study may assist clinicians in the patient-centered shared management of asthmatic children.

Members of the public obtain information about their own or their children's conditions or diseases from different sources, including health professionals (such as treating physicians, physiotherapists, nurses, health educators, pharmacists, or lab technologists,) and media of different types (TV, radio, newspapers, magazines, etc.), but most recently they have come to obtain this information through the Internet. In fact, the context in which patients consume health information has changed dramatically with the diffusion of the Internet, advances in telemedicine, and changes in health coverage in the media.[1] The Internet has proven to be a powerful and very popular vehicle for distributing health information to millions of individuals; it is interactive, user controlled, and provides an effective means for communicating detailed information.[2]

A recent review[3] showed that the majority of health-related Internet searches by the public are for information on specific medical conditions, both before and after the clinical encounter. In fact, patients have been reported to use Internet sources to seek information on many conditions or diseases they may be suffering from, including conditions related to general medical care and family medicine,[4] rheumatological conditions,[5] more serious conditions such as lung cancer[6] and prostate cancer,[7] and even cardiac surgery for congenital heart disease.[8]

This rather new development, reported more frequently within the last 10 to 15 years, has resulted in new horizons for the patient–doctor relationship. In fact, a recent review of current issues in the patient–doctor relationship[9] reported that they include asymmetry of power, perceived challenges to the physician's authority, and interpersonal, systemic, and societal challenges. Concerns also include whether patient access to large volumes of information will improve their health, whether the variable quality of the information will have a deleterious effect, what the effect on health disparities will be, and whether the patient–doctor relationship will improve as patients become equal partners or be damaged if physicians have difficulty adjusting to their new role.[10] Physicians and the organizations that support them must fully understand their role in the e-health revolution. Both must advance their awareness of the "new consumers" and their needs and define specific action items that will help society realize the benefits of e-health.[11]

It is anticipated that the use of the Internet by patients will raise health awareness about their conditions, while its use by physicians will assist their ability to make evidence-based decisions. In asthma management, for example, the challenge is to bridge the gap between excessive morbidity and the science that holds the promise of reducing it; in other words, to translate scientific advances into meaningful recommendations for clinical care and to promote adoption of recommendations.[12]

While there has been increasing use of the Internet in healthcare, minimal research has been conducted to examine what, if any, impact the availability and integrity of healthcare information on the Internet has on the patient–doctor relationship, especially among parents of children suffering from bronchial asthma. Accordingly, this study's objectives were to assess the extent, sources, and effects of Internet use by the parents of asthmatic children in public and private clinics in Riyadh to obtain information related to their children's condition; and to recommend appropriate Internet-based methods for raising awareness of asthma in the community.

SUBJECTS AND METHODS

A cross-sectional approach was used for data collection from a random sample of 500 parents of asthmatic children undergoing treatment at two pediatric pulmonology clinics at King Khalid University Hospital (a

Table 1. Distribution of characteristics and clinical profile of asthmatic children (n=505).

Study variable	Number (%)
Gender (n=486)	
Male	292 (60.1)
Female	194(39.9)
Age (months) (n=466)	
<6	65 (13.9)
7-12	61 (13.1)
13-24	53 (11.4)
25-36	38 (8.2)
37-48	43 (9.2)
49-60	35 (7.5)
>60	171 (36.7)
First diagnosis of asthma (n=485)	
<1 year	264(54.4)
1 to < 3 years	113 (23.3)
3 to < 6 years	61(12.6)
6 to < 12 years	44 (9.1)
>12 years	3 (0.6)
How was diagnosis made? (n=489)	
Physician consultation	393 (81.4)
Nurse consultation	7 (1.4)
Suspected, went for check-up	79 (16.1)
One of the friends advised me	10 (2.0)
How did you locate your physician? (n=482)	
Referral	261 (54.1)
Through a friend	169 (6.1)
From internet	16 (3.3)
Newspaper advertisement	1 (0.2)
Health journals	1 (0.2)
Others	34 (7.1)
Where do you usually obtain medication for asthma? (n=460)	
Hospital	427 (92.8)
Pharmacy	30 (60.5)
Internet	3 (0.65)
How do you communicate with your doctor? (n=483)	
By telephone/SMS	36 (7.5)

Study variable	Number (%)
E-mail	3 (0.6)
Only when I visit the clinic	429 (88.8)
Other	15 (3.1)
How frequently do you communicate with the doctor? (n=488)	
Only when I need to booked an appointment	228 (46.7)
Weekly	4 (0.8)
Monthly	50 (10.2)
Quarterly	152 (31.1)
How frequently do you communicate with the doctor? (n=488)	
Yearly	10 (2.0)
Other	44 (9.0)
Source of information of your child's asthma presentation (n=505)[a]	
Family doctor	35 (6.9)
Pediatrician	189 (37.4)
Pediatric pulmonologist	342 (67.7)
Adult pulmonologist	8 (1.6)
Nurse	67 (13.3)
Pharmacist	3 (0.6)
Internet	61 (12.1)
Health education brochures/posters	55 (10.9)
Radio	4 (0.8)
TV Programs	33 (6.5)
Health Journal	20 (4.0)
Parents of asthmatic children	77 (15.2)
Sources of information of your child's asthma management (n=505)[a]	
Family doctor	28 (5.5)
Pediatrician	166 (32.9)
Pediatric pulmonologist	339 (67.1)
Adult pulmonologist	28 (5.5)
Nurse	69 (13.7)
Pharmacist	12 (2.4)
Internet	49 (9.7)
Health education brochures/posters	30 (5.9)
Radio	4 (0.8)
TV programs	22 (4.4)
Health journal	11 (2.2)

[a] Categories are not mutually exclusive

government teaching tertiary-care setting) and Dallah Hospital (a major private hospital) in Riyadh, Saudi Arabia during the period January to May 2011 . Parents (fathers or mothers) of asthmatic children seeking care at either center who consented to participate in the study were included.

A specially designed questionnaire was used for data collection. This tool included questions about demographic data (for both parents), including nationality, education, occupation, residence, allergy history, and allergy-management practices (as applicable); relevant child information, including age, gender, how the diagnosis was made, medications, communication with treating physician, and sources of information about asthma; and Internet use: location, duration, frequency, search engines used, purposes (eg, asthma presentation, complications, management), usefulness, and limitations. The collected data was reviewed for completeness and accuracy, then analyzed using SPSS version 18.0 (IBM Corp, Armonk, New York, United States). Data management included coding, cleaning, entry, analysis, and presentation. Suitable biostatistical techniques were applied in the analysis (frequency distributions; bivariate analysis using odds ratios, 95% confidence intervals, and *P* values; multivariate analysis using multiple logistic regression). Necessary ethical clearance was obtained from the King Saud University, College of Medicine Institutional Review Board.

RESULTS

Table 1 reflects the distribution of characteristics and clinical profile of the asthmatic children in the study sample (n=505). It shows that most asthmatic children (60%) in our sample were males. A little more than one-third (37%) of them were more than 5 years old. Most of the children (77%) were diagnosed with asthma before their third birthday by a treating physician (78%). The majority of children were seen on referral (54%). It was interesting to learn that most of the parents (85%) reported that they obtained asthma medications from the hospitals where their children were treated and that they only communicated with the treating physician when they visited the clinic (89%). Most parents mentioned that their main source of information about asthma presentation or management was the treating pediatric pulmonologist (67–68%) or the pediatrician (33–37%).

Table 2 shows parent characteristics (n=505). Most parents (90%-91%) were Saudi citizens residing in Riyadh (90%); 23% to 25% had secondary but no post-secondary education and 50% had a university education. Most fathers were in non-health related occupations, whether governmental (52%) or private (37%), with no history of allergy (65%). About two-thirds of mothers were housewives (64%), and about three-quarters had no history of allergy (75%). Among those reporting allergies (25% of mothers and 35% of fathers), most had been diagnosed as asthmatic (68–73%) for which they used either no treatment (34–44%) or salbutamol (39–42%).

Table 3 shows the distribution of asthma-management variables among people who had used the Internet to look up health information (henceforth, "Internet users"; n=400). More than half of the users reported using it for between 10 and 30 minutes (53%), while 22% had used it for less than 10 minutes. Surprisingly, most users (88%) used the Internet for asthma management without being advised to do so by a physician; Google (81%) was the search engine of choice, and general medical websites were the major source of information (88%). Reported reasons for using the Internet for medical information included reassurance (40%), need for clarification of information (38%), and less often, online consultation (19%) and new management techniques (16%). Around 79% of parents reported that the Internet provided solutions to asthma-related questions only sometimes. The most important limitations of Internet use for obtaining asthma-management information included non-availability of Arabic language information (57%) and the highly technical nature of the information (25%), which was not easily understandable. They suggested a need for availability of the following online services: consulting with a treating physician (47%), receiving updates on asthma treatment (38%), booking appointments (32%), chatting with the treating physician (26%); and being directed to specific websites on asthma (24%). When asked if they had attempted to use information from the Internet to discuss their child's condition with the treating physician, most of them (80%) reported that this had never happened, but those who had (20%) felt that the discussion was generally welcomed by the physician concerned (83.5%).

Table 4 includes the results of bivariate analysis testing possible associations between selected study variables and Internet use for asthma information. Only father's level of education (odds ratio=5.1; 95% confidence interval=2.5, 10.5) and mother's level of education (OR=7.6; 95% CI=4.0, 14.5) were found to be predictors for Internet use for asthma information and management. The interaction of father's education and mother's education with Internet use, by stratifying mother's education across two levels of father's education (more and less education) showed a statistically significant association (OR=10.44; 95% CI=4.86, 22.4) of mother's education (at the level of more father education) and Internet use for asthma information when compared with the non-significant association (OR=1.37; 95% CI=0.39, 4.9) of mother's education (at the level of less father's education) and Internet use. (**Table 5**). The multivariate analysis showed the variables nationality of mother ("a non-Saudi mother," OR=4.80; 95% CI=1.1, 21.3) and occupation of mother ("non-health related " OR=2.6; 95% CI=1.9, 3.3) were the independent predictors for Internet use for asthma information and management, as seen in **Table 5**.

Table 2. Characteristics of parents of asthmatic children (n=505).

Characteristic	Father No (%)	Mother No (%)
Nationality (F [n= 493]; M [n= 483])		
Saudi	447 (90.7)	433 (89.6)
Non Saudi	46 (9.3)	50 (10.4)
Education (Fn = 490; Mn = 472)		
Does not read/write	7 (1.4)	14 (3.0)
Reads/writes	11 (2.2)	11 (2.3)
Primary education	22 (4.5)	29 (6.1)
Preparatory education	46 (9.4)	52 (11.0)
Secondary education	115 (23.5)	119 (25.2)
University education	246 (50.2)	235 (49.8)
Postgraduate degree	43 (8.3)	12 (2.5)
Occupation (F [n= 486]; M [n=470])		
Health related	36 (7.4)	31 (6.6)
Non-health related Governmental	252 (51.9)	101 (21.5)
Non-health private	180 (37.0)	29 (6.2)
Housewife	Not applicable	302 (64.3)
Other	18 (3.7)	7 (1.5)
Residence (F [n=469)		
Riyadh	422 (90)	
Near to Industrial area	10 (2.1)	
Other	37 (7.9)	
History of allergy (F [n=450; M [n=464])		
Yes	158 (35.1)	117 (25.2)
No	292 (64.9)	347 (74.8)
If yes, type of allergy (F [n=146]; M [n=112])		
Asthma	106 (72.6)	76 (67.8)
Other	40 (27.4)	36 (32.2)
Drug treatment (F [n=151]; M [n=107])		
None	67 (44.4)	36 (33.6)
Salbutamol (rescue medicine)	59 (39.1)	45 (42.1)
Inhaled Corticosteroid	15 (9.9)	12 (11.2)
Other	10 (6.6)	14 (13.1)

F= sample size of fathers; M= sample size of mothers, but for the same sample of children (n=505).

DISCUSSION

Healthcare delivery is being transformed by advances in e-health and by the newly empowered, computer-literate public, which is ready to become an equal partner in its own health. Such changes can bring about

Table 3. Distribution of asthma management variables among Internet users (n=400).

Variable	No (%)
Time spent on internet for information about asthma (n=325)	
<10 min	69 (21.2)
10 to <30 min	170 (52.3)
30 to <60	49 (15.1
>1 hour	37 (11.4)
Internet use, upon physician advice (n=278)	
Yes	32 (11.5)
No	246 (88.5)
Type of search engine (n=400)	
Microsoft	2 (0.5)
Yahoo	22 (5.5)
Google	324 (81.0)
No response	52 (13.0)
Websites for information related to asthma (n=295)	
Medical base	17 (5.8)
General medical website	259 (87.8)
Specialized medical Journal	11 (3.7)
Other	8 (2.7)
Using Internet for medical purpose (n = 400)	
Need for clarification	154 (38.5)
New management schemes	64 (16.0)
Reassurance	159 (39.8)
Online consulting	76 (19.0)
Internet offered solutions to asthma related questions? (n=344)	
Never	38 (11.0)
Sometimes	271 (78.8)
Always	35 (10.2)
Limitations faced while retrieving information related to asthma (n=400)	
Technical information (not easily understandable)	102 (25.5)
Non-Arabic information	229 (57.2)
Unavailable medicine in Saudi Arabia	14 (3.5)
Others	55 (13.8)
Suggested Internet uses for learning about asthma (n=400)*	
Online consulting with treating physician	188 (47 %)
Online drug purchasing	17 (4.2)
Online booking of appointments	127 (31.8)
Online chatting with my doctor	106 (26.5)
Obtaining updates of asthma	152 (38.0
Being directed to specific websites on asthma	99 (24.8)
Using information from Internet for discussing child's condition with child's doctor (n=359)	
Yes, and he welcomed	60 (16.7)
Yes, and did not welcome	12 (3.3)
Never happened	287 (80.0)

positive results, like improved clinical decision making, increased efficiency, and strengthened communication between physicians and patients.[11] Parents of chronically sick children, such as asthmatic children are no exception. Nevertheless, most parents in our study sample (68%) indicated that information about childhood asthma was obtained from the treating pediatric pulmonologist, which is congruent with the results of a study at the University of Iowa's multidisciplinary thoracic clinic, where 139 patients reported that the most common source of information about their condition was their referring physician (47%) or subspecialist physician (82%).[6] Similarly, data from the US Health Information National Trends Survey[1] indicated that 62.4% of more than 6000 adult patients expressed a high level of trust in their physicians, despite newly available alternative information channels.

Most of the parents in our study sample (79%) reported using the Internet to gain information on their children's condition. This level is higher than that seen in similar studies in Glasgow, on 140 rheumatology patients (43% Internet users);[5] in Texas, on 160 families of children requiring cardiac surgery (58% Internet users);[8] nationwide in the United States, by the US National Health Information Trends Survey of 6369 adults (63% Internet users);[1] and in Detroit, on 1289 patients (65% Internet users).[4] One obvious explanation is that all four mentioned studies were performed 5 to 9 years before ours, when global Internet access and use were generally less prevalent than nowadays, when almost everybody, especially in urban areas, has access to and uses the Internet for several purposes.

The most important predictors for Internet use in our study sample were "higher mother education" (OR=7), "higher father education" (OR=3), the combination of both these higher-education variables (OR=10.44), and "non-health related mother occupation" (OR=2.6). Schwartz et al 2006[4] also reported that education and income of parents were significantly associated with Internet use in their Detroit MetroNet study. Indeed, education is always key to non-traditional channels for seeking professional advice, the classical channel being the treating physician.[4] Parents are increasingly likely, after a diagnosis of their child with asthma, to seek additional information about the disease, its presentations, complications, and modern management strategies—especially highly educated parents. This has been indicated by parents in the current study and other studies.[4-6]

In our study, parents reported the following reasons for Internet use for asthma information: reassurance and clarification (38–40%) and online consultation or obtaining information on new management schemes (16–19%). These reasons seem different from those in the Detroit study,[4] where patients mentioned the following reasons: obtaining information on specific medications (53%), prevention (34%), and alternative therapies (25%). On the other hand, rheumatology patients in the Glasgow study[5] reported looking for relevant informa-

Table 4. Association Between Selected Variables and Internet Use for Child's Asthma (bivariate analysis).

Study variable	Use of Internet		OR (95% CI)	P
	Yes (%)	No (%)		
Nationality of father				
Saudi	348 (77.9)	99 (22.1)	1.0	.021
Non-Saudi	43 (93.5)	3 (6.5)	4.1 (1.2,13.5)	
Education of father				
More education	370 (82.2)	80(17.8)	5.1 (2.5,10.5)	<.0001
Less education	19 (47.5)	21(52.5)	1.0	
Occupation of father				
Health related	30 (83.3)	6(16.7)	1.28 (0.5,3.5)	.74
Non-health related	358 (79.6)	92(20.4)	1.0	
History of allergy (father)				
Yes	129 (81.6)	29 (18.4)	1.1 (0.67,1.9)	.73
No	246 (79.9)	62 (21.1)	1.0	
If yes, type of allergy				
Asthma	84 (79.2)	22 (20.8)	0.81 (0.28,2.24)	.89
Other	33 (82.5)	7 (17.5)	1.0	
Nationality of mother				
Saudi	338 (78.1)	95 (21.9)	1.0	.013
Non-Saudi	47 (94)	3 (6)	4.4 (1.3,14.3)	
Education of mother				
Less Education	22 (40.7)	32(59.3)	1.0	<.0001
More Education	351 (84)	67(16)	7.6 (4.0,14.5)	
Occupation of mother				
Health related	28 (90.3)	3 (9.7)	3.4 (0.96,12.4)	.06
Non-health related	116 (89.2)	14(10.8)	3.0 (1.6,5.9)	.003
Housewife and other	226 (73.1)	83(26.9)	1.0	--
History of allergy (mother)				
Yes	91 (77.8)	26 (22.2)	0.84 (0.5,1.4)	.58
No	280 (80.7)	67 (19.3)	1.0	

Table 5. Predictors of Internet use for asthma information and management (multivariate analysis).

Study Variable	Adjusted OR (95% CI)
Educational status of father (more education)	3.04 (1.25, 7.4)
Educational status of mother (more education)	7.02 (3.3, 14.8)
Occupation of mother (non-health related)	2.6 (1.9, 3.31)

tion (83%), drug treatments (54%), alternative therapies (31%), and patient organizations (11%). A recent literature review[3] summarizes all of the above by mentioning that the Internet is used by the patient before the clinical encounter to seek information to manage the patient's own healthcare independently and/or decide whether they need professional help; after the clinical encounter, however, it is done for reassurance because of dissatisfaction with the information provided by the health professional during the encounter.

The parents in our sample also reported that the Internet sometimes provided solutions to their children's asthma-related questions (79%). This finding is similar to the reports of 83% of rheumatology patients in the Glasgow study[5] and 95% of families of children with congenital heart disease in Texas,[8] who found Internet information useful for understanding their own (in Glasgow) or their children's (in Texas) conditions.

Parents identified two limitations related to Internet use for purposes of managing their children's asthma: the non-availability of information in Arabic (57%) and the highly technical nature of the information, which is not easily understandable by the lay person (25%). In fact, most international societies, including the American Thoracic Society, American College of Chest Physicians, and the European Respiratory Society, have a wealth of information readily available in many languages, but not in Arabic. These include asthma action plans, frequently asked questions (FAQs), asthma presentations, modern management methods, among other things. However, the Saudi Thoracic Society has a special Arabic website called "Breathe," which presents information about asthma management but does not seem to be well disseminated. Our experience is that the site is not well known to many asthma patients or parents of asthmatic children.[13]

Parents in our sample suggested the need for availability of several online resources that would be of benefit for them as parents of asthmatic children, including asthma-information updates (38%) and being directed to specific websites on asthma (24%). Interestingly, 63% of physicians in the Detroit study[4] indicated that they had suggested specific websites to their patients. Furthermore, a recent study[14] investigated the impact of an interactive patient website designed to give asthma patients individual feedback about their condition and to suggest tailored questions for patients to ask their physician. Many patients using this website had a positive shift in their attitudes regarding interactions with their physicians, besides the fact that this usage prompted them to become more actively involved in asthma care.

When the parents in our study were asked if they had attempted to use information from the Internet to discuss their child's condition with the treating physician, they reported that in such cases (accounting for 20% of all respondents) this was generally welcomed by the physician (83.5% of these respondents). A national US telephone survey of 3209 participants[10] indicated that most people who took similar information to the physician (71%) wanted the physician's opinion on the information rather than a specific intervention. The effect of meeting the physician armed with information was likely to be positive as long as the physician had adequate communication skills and did not appear to be threatened by the patient bringing in the information. A recent review[3] indicates that health professionals are responding to the more "Internet-informed" patient in one of three ways: feeling threatened by the information the patient brings and responding defensively by asserting their expert opinion, ("health professional-centered relationship"), collaborating with the patient in obtaining and analyzing information ("patient-centered relationship") or guiding patients to reliable health-information websites ("Internet prescription"), as in the example described above.[14] We believe that for parents of asthmatic children in Saudi Arabia, a mixture of the second and third scenarios, in the presence of easily accessible, user-friendly Arabic websites, would definitely strengthen communication between treating pediatricians and parents of asthmatic children. It would also improve clinical decision making and shared management, leading to better outcomes for children's asthma management, as reported in other studies.[14-16]

The results of this study can be applied to parents of pediatric patients receiving asthma management at academic institutions and private hospital clinics, but cannot be generalized to other healthcare-delivery setups in Saudi Arabia. Further research is needed on larger, more diverse samples, including different healthcare agencies and community sectors, to yield more representative and generalizable results.

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systematic review

An epidemiological analysis of the incidence of osteoporosis and osteoporosis-related fractures among the Saudi Arabian population

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BACKGROUND AND OBJECTIVES: Osteoporosis is common in Saudi Arabia and the burden of management in an aging population will increase in coming decades. There is still no national policy nor consensus on screening for this silent disease. The objective of this analysis was to determine from the published data the prevalence of osteopenia and osteoporosis in Saudi Arabians, the prevalence of secondary osteoporosis, and the prevalence of osteoporosis-related fractures (ORF). We also sought to determine the best age to begin and best modality for screening .

METHODS: Data Sources were MEDLINE (1966 to May 2011), EMBASE (1991 to May 2011), the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (1952 to May 2011), and the Science Citation Index (1966 to May 2011), published data from the Saudi Medical Journal (1985-2011) and Annals of Saudi Medicine (1985-2011). We selected English-language articles with at least 100 Saudi individuals. Two authors independently reviewed articles and abstracted data.

RESULTS: The authors identified 36 potentially relevant articles, of which 24 met the inclusion criteria. Of 5160 healthy women 50 to 79 years of age (mean, SD: 56.8 [2.7]), 36.6% (6.6%) were osteopenic and 34.0% (8.5%) were osteoporotic. In three studies on males (n=822), the prevalence of osteopenia was 46.3% and osteoporosis 30.7%. Males had a significantly higher frequency of osteopenia in comparison to females (P=<.001 95% CI<-0.0333), The mean age of the patients with secondary osteoporosis was 37.4 (13.5, 18-57) years, with the osteoporosis in 46.4% and osteopenia in 34.1%. In 5 studies of ORF, the incidence of vertebral fractures was between 20%-24%.

CONCLUSION: The currently available literature on Saudi Arabian population suggests that the ideal age for screening for low bone mass among the Saudi population should be earlier (55 years) than the ≥65 years in Western countries. Both quatitative ultrasound and dual-energy x-ray absorptiometry could be used for screening. The relatively small number of studies on Saudi Arabians and the different machines used for diagnosis limited the authors ability make conclusions with surety.

Osteoporosis and its related complications are one of the major healthcare problems around the globe. It is estimated that osteoporosis affects about 200 million women worldwide and is a substantial cause of morbidity and mortality. Fifty-four percent of postmenopausal white women are osteopenic and 30% are osteoporotic, and by the age of 80, 27% of women are osteopenic and 70% are osteoporotic.[1] It is reported that about 40% of US white women and 13% of US white men aged 50 years will experience at least one fragility fracture in their lifetime.[2] In 1990s it was realized that the problem of osteoporosis in Saudi Arabia was more severe than in the rest of the world with a reported prevalence between 30% to 48% in this country.[3-9]

Even though safe therapies are freely available for the treatment of osteoporosis and to reduce the risk of fractures,[10-15] most affected individuals are asymptomatic, undiagnosed, and untreated.[16-18] Moreover, the majority of patients at high risk who have already had at least one osteoporotic fracture, are neither identified nor treated adequately.[19] Several organizations, including the US Preventive Services Task Force[20] and International Osteoporosis Foundation[21] recommend screening so as to make an early diagnosis of low bone mass, but in Saudi Arabia still there is no consensus on whom to screen, what age to screen and which modality to use. To be able to make any recommendations, we performed a systematic review to find answers to four questions, which we thought could help in formulating a future plan for Saudi Arabian patients with osteoporosis. First, what is the prevalence of postmenopausal osteoporosis, and male osteoporosis; secondly, how common is secondary osteoporosis; thirdly, what is the incidence of osteoporosis-related fractures (ORF); and lastly, at what age should screening be instituted and which modality used.

METHODS

We searched MEDLINE (1966 to May 2011), EMBASE (1991 to May 2011), the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (1952 to May 2011), and the Science Citation Index (1966 to May 2011), published data from the *Saudi Medical Journal* (1985-2011) and the *Annals of Saudi Medicine* (1985-2011). We supplemented our searches by manually reviewing bibliographies of eligible studies and relevant review articles. The key words selected were Saudi Arabia, osteopenia, osteoporosis and bone mineral density. The inclusion criteria were clinical studies involving at least 100 Saudi Arabian patients or healthy individuals. We included English language studies that diagnosed osteoporosis by radiographs, single photon absorptiometry (SPA), dual photon absorptiometry (DPA), dual-energy x-ray absorptiometry (DEXA) and calcaneal quantitative ultrasound (QUS).

RESULTS

The authors identified 36 potentially relevant articles, of which 24 met the inclusion criteria. Of 5160 healthy women 50 to 79 years of age (mean, SD: 56.8 [2.7]), 36.6% (6.6%) were osteopenic and 34.0% (8.5%) were osteoporotic (**Table 1**). In three studies on males (n=822), the prevalence of osteopenia was 46.3% and osteoporosis 30.7% (**Table 2**). The mean age of the patients with secondary osteoporosis was 37.4 (13.5, 18-57) years, with the osteoporosis in 46.4% and osteopenia in 34.1% (**Table 3**). Males had significantly higher osteopenic in comparison to females (P=<.001 95% CI <-0.0333) Osteopenia in women was 30.7% compared to 44.1% in men. The statistical comparison of osteopenia in women and men was that in 5160 women, osteopenia was reported in 1586, while in men out of 822 the osteopenia reported was in 365. Five studies which reported ORF data showed that the prevalence of femoral fractures in 1991 in men was 71/100 000 and 100/100 000 in women, while in 2007 it was 599/100 000 (men and women). The incidence of vertebral fractures was between 20% to 24% (**Table 4**).

DISCUSSION

Our systematic review of the published data indicate that the prevalence of low bone mass (osteoporosis and osteopenia) in Saudi Arabia is 70.5% in men and women with an average age of 56 years. This suggests that women in Saudi Arabia become osteoporotic earlier than the western women; hence it is recommended that if screening is to be mandated it should be around 55 years of age. The recent census of the Saudi population showed that the number of women aged ≥50 years is 906 526, which suggests that 326 349 (36%) are osteopenic and 308 612 (33%) are osteoporotic. The total population at risk of sustaining an ORF is 634 961. The World Health Organization estimated the prevalence of osteoporosis in Western women (adjusted to 1990 US white women) at any site as 14.8% in women aged 50-59, 21.6% for ages 60-69.[39] Comparing the figures prevalence of osteoporosis in Saudi women is twice that of US white women and their suggestion is to screen women at ≥65 years for osteoporosis is not tenable; hence we believe that the screening for low bone mass in Saudi women should be at least a decade earlier. The analysis of studies published on male osteoporosis showed that the prevalence is similar to the postmenopausal group. Osteopenia in males is reported to be 46.3% while osteoporosis at 30.7%. The average at which the males suffer is at a much younger average age (57.4 [6.3]) years than in western countries. The prevalence of male osteoporosis is 7% in white men, 5% in black men, and about 3% in Hispanic-American men,[40] while osteopenia in US men is reported to be 33% to 47%, which is similar to the 44.1% in the Saudi male population.[41] Even in the male Saudi population we tend to believe that screening should be instituted earlier than recommended by the Western criteria.

Secondary osteoporosis, which is caused by various disorders, metabolic derangements, drug administration and can be chemotherapy induced due to malignancies, still remains underdiagnosed and undertreated. Romagnoli et al[42] reported the prevalence of primary osteoporosis to be significantly higher than secondary osteoporosis in both men and women. In our patients, secondary osteoporosis occurred in a young age group

Table 1. Studies with data on postmenopausal Saudi women.

Studies	No. of patients	Age (y)	Methodology	Osteopenia n (%)	Osteoporosis n (%)
Al-Habdan et al (2009)[5]	3311	55.6	Ultrasonography	948 (30.3)	720 (23)
Ardawi et al (2005)[7]	220	50-79[a]	DEXA	95 (43.4)	62 (28.2)
Sadat-Ali et al (2004)[9]	256	57.6	DEXA	79 (31)	107 (42)
ElDesouki (2003)[6]	830	59	DEXA	254 (30.6)	(328) 39.5
El Desouki (1999)[22]	283	52-62[a]	SPA	(96) 34	68 (24)
Sadat-Ali et al (1996)[4]	150	54.1	SPA	68 (45)	60 (40)
Sadat-Ali et al(1993)[3]	110	58	Radiographs	46 (42)	45 (41)

DEXA: dual-energy x-ray absorptiometry, SPA: single photon absorptiometry. Age data are mean and standard deviation. [a]mean age and SD not available in the publication

Table 2. Studies with data on male osteoporosis.

Studies	No. of patients	Age (y)	Methodology	Osteopenia n (%)	Osteoporosis n (%)
El-Desouki and Sulaimani (2007)[23]	429	53 (12.6)	DEXA	158 (36.9)	101(23.5)
Sadat-Ali and Al-Elq (2006)[24]	115	61.8 (1.8)	DEXA	55 (47.9)	35(30.8)
Ardawi et al (2005)[7]	278	50-79[a]	DEXA	150 (54.1)	105(37.8)

DEXA: dual-energy x-ray absorptiometry. Age data are mean and standard deviation. [a]mean age and SD not available in the publication

Table 3. Reports on secondary osteoporosis.

Studies	Age (y)	No. of patients	Primary disease	Methodology	Osteopenia n (%)	Osteoporosis n (%)
Sadat-Ali et al (2011)[25]	28.4	186	Sickle cell disease	DEXA	30 (16)	135 (72.5)
Al-Turki H (2009)[26]	27.5	35	Sickle cell disease and pregnancy	DEXA	14 (39.8)	21 (65)
Al-Amri and Sadat-Ali (2009)[27]	49	71	Postchemo-therapy	DEXA	24 (33.9)	19 (26.8)
Sadat-Ali et al (2008)[28]	30	87	Sickle cell disease	DEXA	22 (25)	27 (31)
Sadat-Ali et al (2009)[29]	38.3	165	Steroid use	DEXA	81 (49.1)	48.3
Sadat-Ali et al (2008)[30]	18	32	Scoliosis	DEXA	9 (28.1)	20 (62.5)
Sadat-Ali and Al-Elq (2007)[31]	33	36	Sickle cell disease	DEXA	7 (19.5)	14 (38.9)
Al-Elq and Sadat-Ali (2006)[32]	57.5	154	Diabetes mellitus	DEXA	80 (52)	40 (26)
Al-Maatouq et al (2004)[33]	55	101	Diabetes mellitus	DEXA	44 (43.6)	47 (46.8)

DEXA: dual-energy x-ray absorptiometry.Age data are mean and standard deviation (when available).

Table 4. Data related to osteoporosis-related fractures.

Studies	No. of patients	Sex	Methodology	Site of Fractures	n (%)
Sadat-Ali et al (2011)[34]	980	Male	Retrospective	Vertebral	157 (13.1)
Al-Osail, Sadat-Ali et al (2010)[35]	165	Male and female	Retrospective	All	25 (15.2)
Sadat-Ali et al (2009)[36]	785	Female	Retrospective	Vertebral	159 (20.3)
Bubshait and Sadat-Ali (2007)[37]	4910	Male and female	Retrospective	Proximal Femur	138 (2.8)
Al-Nuaim et al (1995)[38]	203 000	Male and female	Retrospective	Proximal Femur	103 (0.05)

(mean age and SD, 37.4 [13.5] years) and higher than primary osteoporosis in men and women (46.4 [16.1] to 31.9 [1.6], $P<.001$, 95% CI<-13.4486). This comparison suggests that patients with known diseases and on medications which cause osteoporosis should be screened earlier, to institute early therapy and prevent complications of ORFs.

Five studies on ORF reported 582 fractures in 2 071 400, making an incidence of 280 fractures per 100 000 population. A recently published study by Brauer and colleagues[43] concluded that in the US the annual mean number of hip fractures was 957.3 per 100 000 for women and 414.4 per 100 000 for men. Our analysis shows that the annual prevalence of all ORF was 277.4/100 000. The prevalence reported in 1995 for femoral fractures was 50.7/100 000 and by 2007 the population of ≥50 years men and women was 164 128 and the number of femoral fractures was 984, giving a yearly prevalence of 599/100 000. Such an increase was observed in other countries as well due to aging of the population. Figures from United Kingdom showed the age-standardised incidence rates of fracture femurs increased by 32% in women and 38% in men,[44] while Koh et al[45] reported that hip fracture rates from 1991 to 1998 were 152/100 000 in men and 402/100 000 in women, and this was 1.5 and 5 times higher than corresponding rates in the 1960s. With the aging of the Saudi Arabian population, the number of fractures is expected to rise unless appropriate screening measures and adequate treatment is given.

Various methodolgies have been used for screening for osteoporosis in different parts of the world. Currently, DEXA is the method of choice for measuring bone mass in the axial skeleton and is used for making a diagnosis of osteoporosis. DEXA allows accurate diagnosis of osteoporosis, estimation of fracture risk and monitoring of patients undergoing treatment. Additional features of DEXA include measurement of bone mineral density at multiple skeletal sites, safety of performance, short investigation time and ease of use.[46-48] The use of QUS of the calcaneum came into vogue, to predict fracture risk due to low bone mass on the basis of calculation of the stiffness index, broadband ultrasound attenuation, speed of sound velocity, and T-score. The QUS is an inexpensive, radiation free, portable, and may provide information on bone quality and bone structure. Recently a new reference value for the diagnosis of low bone mass for the Saudi population has been assessed and reported.[49] The reported sensitivity and specificity of the QUS in detecting low bone mass is around 90%.[50,51] Studies also supported its routine use to predict fracture risk due to low bone mass.[52,53] At present in Saudi Arabia, approximately 30% of women aged ≥56 years, 30.7% of men aged ≥60 years are expected to have osteoporosis and 25 percent of these women will develop a vertebral deformity due to fractures of the spine, and half of them will end up having a hip fracture.

The authors thus conclude that screening for postmenopausal woman in the Saudi Arabian population should start at the age of 50 years and for male osteoporosis at 55 years so that early preventive measures may be instituted. An awareness program is needed to stress the need for early diagnosis of secondary osteoporosis. We further believe that screening either by ultrasound or DEXA could be used (though DEXA is more accurate and precise).

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case report

Recurrent trichilemmal carcinoma with a large cutaneous horn formation

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We describe an unusual case of trichilemmal carcinoma accompanied by a large horn formation in a 79-year-old man who presented with a brown tumor mass including a 15-cm-long horn on the vertex for one and a half years. Two months after the surgical removal of the primary tumor, the tumor recurred with a dimension 10×8×8 cm. The tumor was then excised again and the wound was covered using skin from the patient's back. Microscopically, the tumor showed histology consistent with trichilemmal carcinoma. After 2 years, the patient had not shown any recurrence or metastases. We highlight the features that distinguish trichilemmal carcinoma from the other malignant tumors, such as squamous cell carcinoma, basal cell carcinoma, nodular melanoma, or keratoacanthoma.

Trichilemmal carcinoma is a rare cutaneous tumor that is usually solitary and occurs in the sun-exposed areas of elderly individuals.[1] Dozens of case reports of this malignancy have been published. We report an unusual case of trichilemmal carcinoma with a large horn formation. After the surgical removal of the primary tumor, the recurrent tumor was excised again, and the patient has not experienced further recurrence or metastases over the past 2 years.

CASE

A 79-year-old man presented with a brown tumor mass on the vertex of his head, which had been present for one and a half years. Initially, the tumor appeared as a small brown nodule with no obvious inducements, and one and a half years later, the nodule was 15 cm long and resembled a horn (**Figure 1A**). Soon after that, the tumor appeared to be ulcerated and accompanied by bleeding with the appearance of grayish-white mucous material. The patient felt pain and sought medical attention. The surface of the tumor horn was removed. Two months after the surgery, the tumor reappeared with a dimension 10×8×8 cm and was bleeding (**Figure 1B**). The patient's medical history showed that he had diabetes for 1 year and hypertension for 3 to 5 years. The patient did not have a significant head injury or trauma; however, he had evidence of alcohol and tobacco use, and a history of significant sun exposure throughout his life. Physical examinations revealed that the patient's heart, lung, and abdomen were functioning normally. Laboratory tests revealed high fasting blood glucose levels (12.11 mmol/L, normal range 3.9-6.1 mmol/L); however, other blood and urine tests were normal. A chest radiograph did not indicate any metastatic nodules. Skin examinations found the previously described tumor mass on the vertex, but no enlarged superficial lymph nodes.

The tumor was surgically excised and the wound was covered using the back trunk skin-grafting dermatome (**Figure 1C**). The tumor specimen was fixed in formalin and embedded in paraffin. Five-micron-thick sections were cut and stained with hematoxylin and eosin. Under the microscope, the tumor showed a lobular formation and plate-like growth of glycogen-rich clear cells with variable glycogen vacuolation, which were often surrounded by palisading cells and central keratinization (**Figure 2A,B**). Keratinaceous microcysts and small squamous eddies were also noted in the center of the lesion. The palisading basal cell layer resembled the external root sheath of hair follicles **Figure 1B**. A periodic acid-Schiff (PAS) stain-positive and diastase-resistant thickened basement membrane was partially

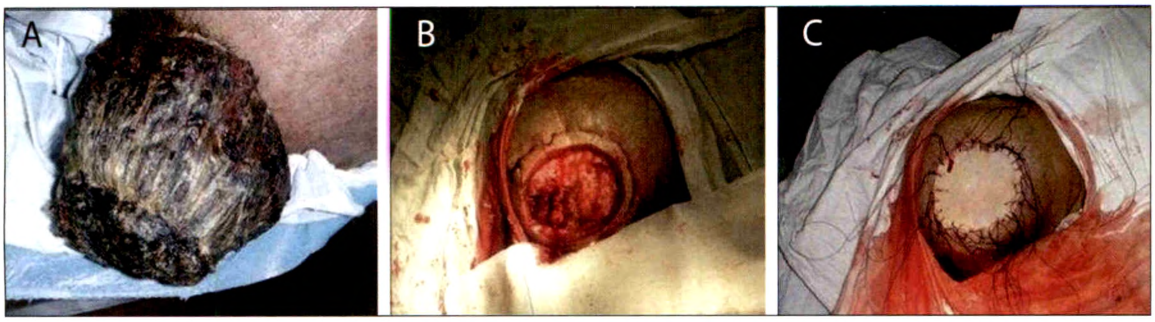

Figure 1. A. The primary tumor. The tumor mass with a 15-cm long horn shows bleeding and grayish-white mucous ulceration. B. The recurrent tumor. The tumor is 10 cm long. C. After excision, the wound was covered by using a back trunk skin-grafting dermatome.

surrounding the tumor cells (**Figure 3A**), and one or more hair follicles were always present. The tumor cells showed markedly atypical cellular and nuclear morphology **Figure 1B**. The immunostaining showed that pancytokeratins AE1/3 and cytoplasmic tyrosine kinase (HCK) (**Table 1**) were present in the tumor cell cytoplasm (**Figure 3B**), but CAM5.[2] and cytokeratin 7 (CK7) (**Table 1**) staining were both negative (**Figure 3C**). Therefore, a diagnosis of trichilemmal carcinoma with a large cutaneous horn formation was made. After the surgical removal of the primary tumor, the recurrent tumor was excised again, and the patient did not experience further recurrence or metastases over 2 years.

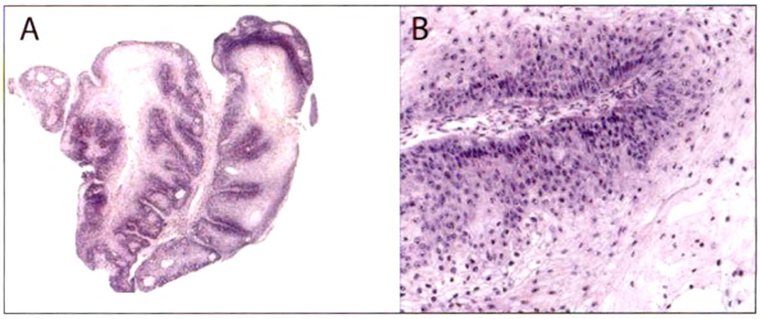

Figure 2. Tumor histology. HE stain shows lobular formation or plate-like growth of clear cells with keratinaceous microcysts and small squamous eddies. Marked cellular and atypical nuclei are present in tumor cells (A ×40, B ×100)

Table 1. Antibodies used for immunohistochemistry during the study.

Antibody	Source and catalog number	Dilution
AE1/AE3	DAKO, M3515	1:200
CAM 5.2	Becton Dickinson, 349205	1:2
Cytokeratin 7	DAKO, M7018	1:100
HCK	DAKO, 34 beta E12	1:150

DISCUSSION

Trichilemmal carcinoma is a rare skin tumor that originates from the external root sheath of the hair follicle and is the malignant form of the usually benign trichilemmoma. The patient presented with a fast-growing tumor that reached 10 cm in 2 months after the primary tumor was excised. However, 2 years after excision for a second time, the tumor has not shown any metastasis. Therefore, a differential diagnosis is very important to distinguish it from the other malignant tumors, such as squamous cell carcinoma (SCC), basal cell carcinoma, nodular melanoma, or keratoacanthoma. These malignant tumors are more aggressive than trichilemmal carcinoma; they have a slower growth rate but a very distinct histology. In addition, a trichilemmal carcinoma is usually a solitary lesion, occurring separately from the proliferating trichilemmal tumor (PTT).[1]

Morgan et al[2] reported the results of immunohistochemical tests of 12 spindle cell SCC samples. The immunohistochemical battery consisted of CK7, pancytokeratins AE1/AE3, HCK (34 beta E12), and low-molecular weight keratins (CAM 5.2). The results were as follows: 34 beta E12 (12/12 samples, 100%), p63 (10/12, 80%), AE1/AE3 (8/12, 67%), and CAM 5.2 (7/12, 58%). The authors concluded that 34 beta E12 was the most promising cytokeratin for distinguishing spindle cell squamous carcinoma from the histological mimickers, such as, AFX (atypical fibroxanthoma), spindle cell/desmoplastic melanoma, scar, and cutaneous leiomyosarcoma. Du et al[3] reported a case of extramammary Paget disease mimicking acantholytic SCC in situ. The immunohistochemical staining showed a carcinoembryonic antigen (CEA), CK7, and cCK8 to be strongly expressed in the nests and singly arranged large tumor cells, and the surrounding epidermis was positive for CK5/6 and negative for CEA. In our case, we differentiated trichilemmal carcinoma from SCC by hematoxylin and eosin and PAS staining pattern.

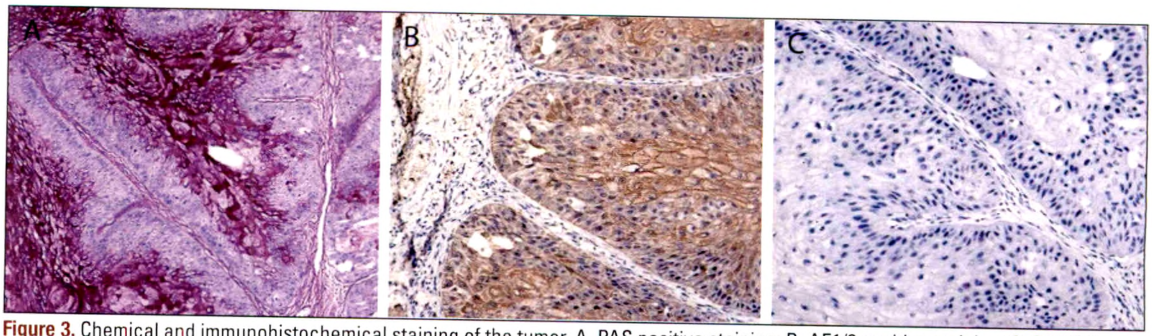

Figure 3. Chemical and immunohistochemical staining of the tumor. A. PAS positive staining; B. AE1/3 positive staining; C. CAM5.2 negative staining. Paraffin sections were prepared and subjected to chemical (for PAS) or immunohistochemical analyses. The antibodies used are listed in Table 1.

Immunohistochemistry revealed that AE1/3 and HCK (**Table 1**) were positive, but CAM5.[2] and CK7 (**Table 1**) were negative, strongly indicating trichilemmal carcinoma.

Malignant proliferating trichilemmal tumor (MPTT) is considered to be a malignant transformation of a PTT. Morphologically, MPTT has more extensive hyperkeratosis and a greater number of cysts than malignant trichilemmoma.[4] The incidence of recurrence or metastasis of MPTT is considered to be similar to that of SCC on burn scars. In terms of its general clinical features, MPTT mainly occurs on the scalp or face in elderly men. MPTT may be accompanied by ulceration, papillate formation, agglutination of slough, or rapid enlargement and is sometimes difficult to differentiate from SCC.[5] The MPTT histology is characterized by the presence of clear cells with atypical nuclei and trichilemmal keratinization of tumor cell nests,[4] and tumor cells are commonly PAS positive. There have been several reports of regional and distant metastases,[6] and fatal cases have also been recorded. Amaral et al[7] reported an inguinal case that, after surgical resection of the tumor, resulted in fatal metastasis. Hodl et al[8] reported a case with invasion and penetration of the cerebral sinuses, and the diagnosis of MPTT was made by the presence of trichilemmal keratinization and clear cells with atypical nuclei. Radiation or chemotherapy is used to treat MPTT, but the effectiveness of such treatments is unknown.[5] Local excision with removal of the regional lymph nodes and follow-up is usually the best treatment course option.

Schell et al[9] reported eleven cases of trichilemmal carcinoma and found that the tumor often occurred in the slightly damaged skin of elderly people. Its clinical appearance was nonspecific, but histologically, trichilemmal carcinoma is differentiated from trichilemmoma by the occurrence of markedly increased atypical nuclei and disordered tissue architecture. Although the histology of trichilemmal carcinoma indicates a high-grade malignancy, its biological behavior appears to be relatively benign. Furthermore, Swanson et al[10] analyzed the histological and clinical findings in 10 cases of trichilemmal carcinoma and found that, in every case, the tumor occurred in the hair-bearing and sun-exposed skin, and involved the scalp, face, trunk, or upper extremities. The lesions were usually slightly raised, pale, tan, or reddish, and keratotic. The tumor size was usually 0.4 to 2.0 cm with less than 1-year history. All patients were treated by a wide local excision and, neither recurrence nor metastasis was reported after 11 to 92 months of follow-up. Histologically, the tumors were composed of a lobular proliferation centered on the pilar apparatus. Tumor cells have a predominately glycogen-rich, mucin-negative, with clear or pale eosinophilic cytoplasm. The involvement of the interfollicular epidermis was invariably noted, with a superficial ulceration in 7 tumors. Transitional zones between trichilemmal carcinoma and the adjacent epidermis were not present, although pagetoid spread occurred in 2 examples. Invasion of the reticular dermis was present in 8 cases, with infiltration to the mid-dermis in 5. All tumors exhibited areas of trichilemmal-type keratinization, and dyskeratotic cells were present in 6 patients. Hyperkeratosis and parakeratosis were variably present as well. Actinic damage was a constant feature. Despite local invasion at diagnosis, the clinical course of trichilemmal carcinoma was indolent in all cases.

Wong et al[11] reported 13 cases of trichilemmal carcinoma with similar characteristics as the cases described by Swanson et al.[10] However, several reports indicate that trichilemmal carcinoma does occur in unexposed parts of the body, accompanied by metastasis. For example, Knoeller et al[12] reported trichilemmal carcinoma at the right distal thigh, and a metastatic tumor was found in the right inguinal lymph nodes. Five years after initial diagnosis and surgery, a metastasis to the left tibia and fibula occurred. Allee et al[13] described a case of multiple recurrent trichilemmal carcinoma with perineural invasion. The outer root sheath differentiation of the neoplasm was confirmed using antibodies against cytokeratin 15 and 17 and c-erb-B2. The trichilemmal carcinoma demonstrated abundant cytoplasmic staining of cytokeratin 17 and c-erb-B2. The aggressiveness of the tumor was evident by tumor neurotropism and failure of multiple surgical excisions. Several more cases have been reported recently,[14-18] suggesting that there may be an increased incidence of trichilemmal carcinoma.

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case report

Intravenous immunoglobulin-associated renal failure in a patient with post-transfusion purpura

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Intravenous immunoglobulin (IVIG), initially developed for immunodeficiency disorders, has now been used for multiple autoimmune diseases and infections. These are generally well tolerated, with few adverse effects. Acute kidney injury has been described in very rare instances. We report an interesting case of a 59-year-old African American male with a pertinent history of diabetes mellitus, hypertension, endocarditis, and peripheral vascular disease, who was diagnosed with post-transfusion purpura. He was then treated with IVIG and subsequently developed an acute worsening of renal function in a time span of 3 days. The etiology remained elusive even after an extensive workup. Renal biopsy was done finally, which showed findings suggestive of osmotic nephropathy that was traced to the sucrose used as a stabilizing agent in the IVIG. In light of the increasing use of IVIG, it is therefore highly recommended that clinicians are well aware of this side effect of IVIG.

Intravenous immunoglobulin (IVIG) is a highly purified immunoglobulin G preparation made from pooled human plasma. It is usually prescribed for a variety of conditions that include hematological, autoimmune, and infectious diseases. The initial use of IVIG was hampered by the large incidence of adverse effects like chills, back pain, and fever. This was largely believed to be secondary to the immune complexes activating the complement system. Stabilization with products like sucrose, maltose, glycine, sorbitol, or albumin helped avert these side effects. Renal failure has been reported as a rare complication accounting for <1% cases of the IVIG therapy.

CASE

A 59-year-old African American male with a medical history significant for hypertension, diabetes mellitus, and extensive peripheral vascular disease was admitted with left toe gangrene and complete occlusion of the femoropopliteal bypass graft. The patient underwent an amputation of the left knee. He received 2 units of packed red blood cells (PRBCs) because of the blood loss related to the procedure. His postoperative course was complicated with fevers and methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia and aortic valve endocarditis. He was started on intravenous vancomycin therapy and discharged. Two days later, he was admitted with complaints of persistent fevers despite being on vancomycin. The physical examination at the time of admission revealed that the patient was febrile with a temperature of 101.4°F. The systemic examination did not seem to show any obvious source of infection. The diagnostic workup included routine labs, blood and urine cultures, and x-rays. These were all negative except for a platelet count of 18×10^9/L (reference range, 150-400$\times10^9$/L). These dropped to 4×10^9/L by day 3 with no evidence of any spontaneous bleed. Heparin-induced thrombocytopenia (recent use of heparin), endocarditis, and vancomycin-related side effects were considered among other differentials. Withholding heparin and vancomycin did not improve the clinical picture. We also kept the possibility of post-transfusion purpura in view of the recent history of transfusion of PRBCs. His results revealed negative HIT antibody and positive human platelet alloantigen antibody (anti-HPA-1a) to confirm the diagnosis of

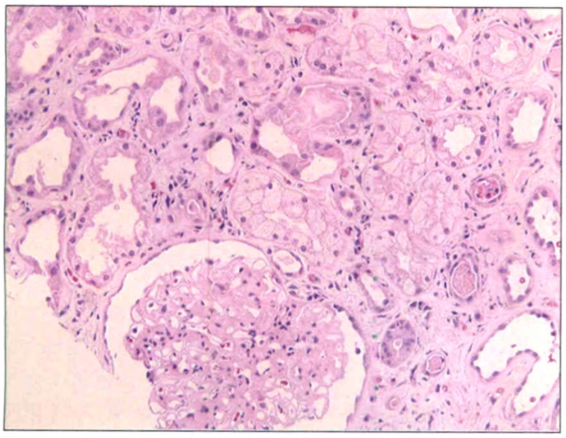

Figure 1. Vacuolization and swelling of the proximal tubule consistent with osmotic nephropathy (H&E, ×100).

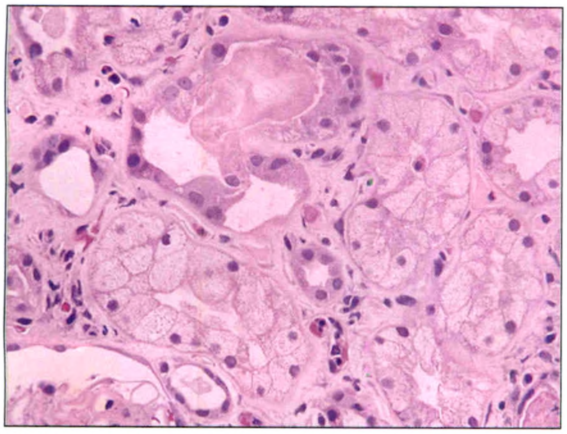

Figure 2. H&E stained specimen showing proximal tubular vacuolization (×400).

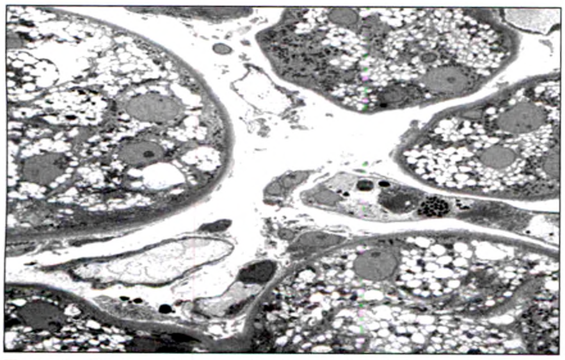

Figure 3. Electron microscopic picture showing osmotic nephropathy.

post-transfusion purpura. He was immediately started on a high dose of IVIG (Carimune NF ZLB Behring AG, Berne, Switzerland) with subsequent improvement in the platelet count. Unfortunately, within 3 days of starting IVIG, the patient showed worsening kidney function. Serum creatinine increased from 1.4 to 6.6 mg/dL (reference range, 0.4-1.1 mg/dL) with oliguria. The underlying cause of this renal failure was still elusive even after a detailed workup. Considering the timeline of onset of renal failure with the administration of IVIG, the diagnosis of IVIG-induced nephropathy was entertained among differential diagnoses. The diagnostic workup ended in a renal biopsy (**Figures 1-3**) that showed findings suggestive of osmotic nephropathy, which was traced to the sucrose used as stabilizing agent in the IVIG. The IVIG was withdrawn. His renal function and urine output improved to baseline over the next 7 to 10 days.

DISCUSSIONS

Renal failure has been reported as a rare complication accounting for <1% cases of IVIG therapy. Only few case reports are available that describe this entity. The analysis of previous case reports suggest that renal adverse effects occurred in the first 10 days after initiation of therapy, with a mean of 3 days and a peak of creatinine around day 5. To make a diagnosis, a temporal association has to be established with the administration of IVIG. A clinical diagnosis is made after ruling out other causes and is confirmed with renal biopsy.[2,3]

It has been suggested that the mechanism underlying the IVIG-induced renal failure is a result of the effect of the osmotic load posed to the proximal tubules by the sucrose content of the IVIG preparation. The absence of the sucrase enzyme at the brush border of the proximal tubular cells results in high concentrations of sucrosethat eventually result in pinocytosis of sucrose into the cells. This is followed by water and causes it to swell resulting in cytoplasmic vacuolization and degeneration of proximal tubular cells.[4,5] This is reiterated by the fact that most of the case reports (90%) in an FDA report and 78% in a review of the published studies by Orbach et al of IVIG nephropathy involved sucrose as the stabilizing agent. Of note, the incidence of renal failure when maltose was used as the stabilizing agent was also very low, probably secondary to the fact that the maltase enzyme is present in the brush border of proximal tubular epithelial cells.[6] Furthermore, the findings in biopsy results are identical to those seen in human beings and animals with sucrose nephropathy. Other mechanisms have also been suggested for the osmotic injury caused (a) by enhancing the tubuloglomerular feedback resulting in afferent arteriolar constriction and a decline in filtration pressure and (b) severe renal artery constriction causing a decrease in glomerular filtration rate.[7]

In reviewing the course of ARF after IVIG, most cases resolved spontaneously. About 36% of the patients required hemodialysis. The duration of renal failure was between 3 to 45 days. The average duration was 13 days with the creatinine usually reaching the baseline in 7 to 15 days.[8] Some of the risk factors for developing the IVIG-induced renal failure include increased age (>65 years), impaired renal function at baseline, dehydration, high-dose IVIG therapy (400-2000 mg/kg), use of sucrose stabilizer, and the rate at which the IVIG is administered. Diabetes mellitus, diuretic use, and concomitant nephrotoxic drug administration have been also cited as risk factors.[3-5,7]

Our patient showed onset of renal failure by the third day, with the creatinine peaking on the eighth day followed by a return to baseline renal function within 15 days. The IVIG used was Carimune NF (1.67 g sucrose/g protein). Even though his age was 59 years, which is slightly below the average age group (generally >65 years age), he had other risk factors such as impaired renal function, diabetes mellitus, and the use of sucrose stabilizers in the IVIG administered. Fortunately, his renal function improved spontaneously without the need for hemodialysis. Of note, Carimune NF or Sandoglobulin (ZLB Behring AG, Berne, Switzerland) has the highest sucrose content among the conventional IVIGs used. As in the other cases described, biopsy findings were consistent with osmotic injury similar to sucrose nephropathy.[7]

To summarize, in general, recommendations are to use sucrose-containing IVIG preparations with caution and switch to other agents when risk factors are present. Adequate hydration along with avoidance of other nephrotoxic medications and diuretics is recommended. Using the smallest dose possible as well as prolonging the infusion interval also helps minimize the brunt of renal injury caused.

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Ectopic nephrogenic rest in the inguinal canal in a 6-month-old girl and a review of published studies

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Ectopic nephrogenic rests in the inguinal canal are rare. Usually discovered incidentally during surgery, these rests should raise the suspicion of an early extrarenal Wilms tumor. The differential diagnosis between the two entities is not only difficult but also essential, since they imply different treatment decisions. We report a rare case of an inguinal ectopic nephrogenic rest found in a 6-month-old girl and discuss the clinicopathological implications of this condition. The patient was admitted for a routine repair of a presumed inguinal hernia; during suregry, a nodular mass was noted in the inguinal canal. Pathological diagnosis confirmed the diagnosis of an extrarenal hyperplastic nephrogenic rest. Five previous cases of ectopic nephrogenic rests originating in the inguinal canal have been reported, all of which were associated with a patent processus vaginalis. In this case, the nephrogenic rest was not associated with a congenital inguinal hernia.

Ectopic nephrogenic rests (ENRs) are extremely rare lesions that may occur in any location between the chest wall and the scrotum. Sometimes confused with early extrarenal Wilms tumors (WTs), ENRs can present difficulties in differential diagnosis, which will have an impact on patient management and affect prognosis. To date, only five cases of ENR located in the inguinal canal have been reported in published studies in pediatrics.[1-4] We report the case of an inguinal ENR and discuss the practical diagnostic difficulties that a clinician faces when dealing with an incidentally found nephrogenic rest.

CASE

An apparently healthy 6-month-old girl was admitted for routine repair of a presumed right inguinal hernia. At surgery, a 2.5-cm nodular mass was noted in the inguinal canal close to the internal ring; no hernial sac was found. Complete resection of the mass was accomplished. Grossly the resected specimen measured 2.5×1.5×1.0 cm with a nodular external surface. At dissection, the cut surface of the tumor was whitish and of soft rubbery consistency and showed focal hemorrhage without necrosis. Microscopically, the lesion was composed of cellular nodules; no atypical mitoses or anaplastic elements were observed. These nodules were characterized by the presence of embryonal renal tubules, focal fetal glomeruli, cystic spaces lined by columnar or cuboidal cells, and the presence of nests in papillary structures protruding into the cystic spaces (**Figure 1**). At the periphery of the lesion, there were clusters of fetal glomeruli, embryonal tubules, small blastemal nests, and psammoma bodies in gradual transition to the cellular nodules without a limiting fibrous capsule (**Figures 2a, b**). The initial pathologic interpretation indicated a nephrogenic embryonal hyperplastic lesion with features more compatible with those of an extrarenal proliferative nephrogenic rest. The lesion was difficult to distinguish from a favorable histology extrarenal WT. Further diagnostic evaluations including abdominal and renal ultrasonography were negative for primary renal tumor or heterotopic nephrogenic rest in other sites. The chest radiography findings were normal. The final pathological diagnosis concluded it was an extrarenal hyperplastic nephrogenic rest as confirmed by the Nephroblastoma Pathology Panel/International Society of Pediatric Oncology. A pediatric hematologist and oncologist were consulted, a "watchful waiting" approach was adopted, and the patient was

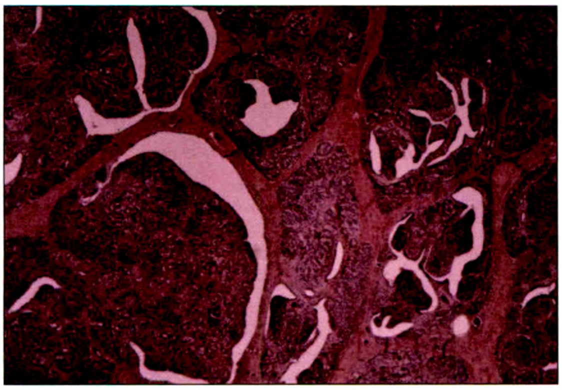

Figure 1. The lesion composed of cystic spaces lined by tubular columnar epithelial cells and nodules composed of blastemal nests and tubules. The nodules surround and protrude into the cystic spaces.

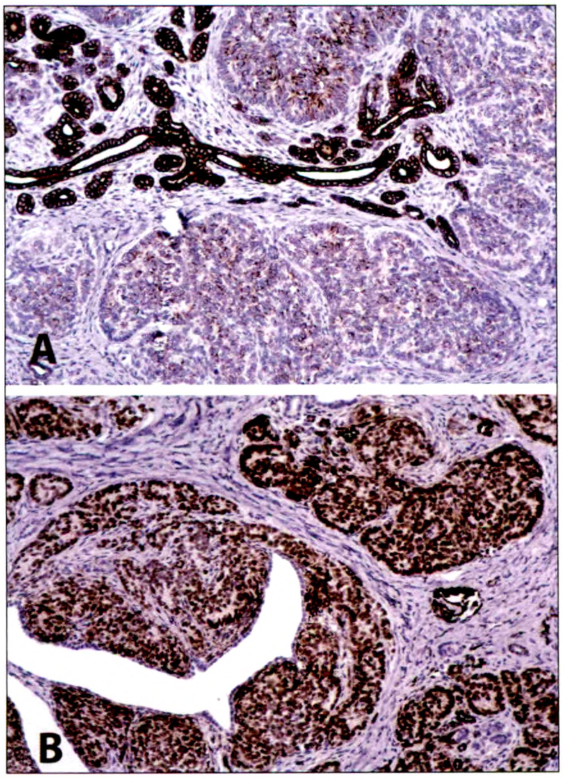

Figure 2. A) WT-1 immunohistochemical expression in the nuclei of the blastemal cells and the fetal glomeruli. No expression of WT-1 in the nuclei of the cells lining the cystic space. B) Strong immunohistochemical expression of cytokeratin 8.18 in the tubules and the faint dotlike detection of the antigen in the blastemal cells.

closely followed up with a surveillance ultrasound every 6 months. Eighteen months after the surgery, the patient was doing well; her follow-up ultrasound scans were negative without any evidence of local recurrence.

DISCUSSION

The most common lesions encountered incidentally during surgery in the inguinoscrotal region are ectopic adrenal tissue remnants. The overall incidence of the adrenocortical remnants varies from 1% to 9.3% in children undergoing inguinal operations. These rests present as bright yellow nodules (1-5 mm in diameter), and once recognized should be removed as they may undergo marked hyperplasia or neoplastic changes.[5] Less frequently, malignant lesions such as neuroblastoma, rhabdomyosarcoma, or mesothelioma may be found in the inguinal region.[1] ENRs have been reported in several locations including the heart, thorax, colon, adrenal gland, and lumbosacral area.[6] A location in the inguinal canal is extremely rare; this is only the sixth case of an inguinal ENR reported in the pediatric age group (**Table 1**). Interestingly, all previous cases of an inguinal ENR reported in published studies have been associated with a patent processus vaginalis. The present case is unique as much as the ENR was not associated with a congenital inguinal hernia. Nephrogenic rests appear to develop from a persisting nephrogenic blastema beyond 36 weeks' gestation when nephrogenesis ceases, and they consist of blastema, epithelial elements, and variable amounts of stroma. Most ENRs undergo maturation, sclerosis, and spontaneous regression; some remain unchanged in size and composition whereas others may progress toward hyperplastic proliferation. Only a minority of nephrogenic rests will undergo neoplastic transformation into either benign adenomas or WTs (1:100 cases). This malignant transformation is most likely the result of a WT1 (11p) gene mutation. Genetic studies have shown that nephrogenic rests often present many of the same chromosomal defects as a WT, supporting the theory that they are precursor lesions to nephroblastoma.[7]

Distinguishing between ENR and extrarenal primary, WTs are essential since these entities imply different prognoses and treatment management. Certain criteria should be fulfilled before a lesion can be regarded as an extrarenal WT. The histologic structure of the lesion should confirm the presence of a primitive blastematous spindle or round cell component and provide evidence of abortive or embryonic tubular or glomeruloid structures. Extrarenal WTs are usually round-shaped, form a fibrous pseudocapsule around the lesion, and show atypical mitoses or anaplasia.[7,8] Specifically, a nephrogenic rest resembles a favorable histology WT; no clear pathologic separation of the two is observed. In the present case, the nodular pattern and the gradual transition of resting embryonal clusters to cellular blastemal nodules without a dissecting limiting fibrous capsule leaned

Table 1. Clinical data of inguinal ectopic nephrogenic rests in published studies.

Reference	Age	Gender	Presentation	Treatment	Follow-up	Outcome
1	14 months	M	Nonpalpable testis	Excision	6 months	Recurrence (Extra renal Wilms tumor)
2	8 months	M	Nonpalpable testis	Excision	18 months	No recurrence
3	2 months	M	Nonpalpable testis	Excision	--	No recurrence
4	5 days	F	Inguinal hernia	Excision	9 months	No recurrence
5	5 days	F	Inguinal hernia	Excision	40 months	No recurrence
Present case	6 months	F	Inguinal hernia	Excision	24 months	No recurrence

more toward ENR. However, the infiltrative margin of the lesion, the considerable blastemal component, and the immunohistochemical detection of skeletal muscle fibers represented features of nephroblastoma. The absence of atypical mitoses or anaplastic elements excluded the diagnosis of an established small WT or an anaplastic nephrogenic rest. In addition, as no "overgrowth" of any component was noted, the lesion was diagnosed as a hyperplastic nephrogenic rest rather than an established tumor.

At present, there is no consensus regarding the optimal therapeutic management of a child with an ENR. If the diagnosis is not clear and an extrarenal WT is suspected, the use of stage III guidelines for chemotherapy and radiotherapy is recommended while some authors suggest hyperplastic nephrogenic rests be treated similarly to stage I WT to decrease the risk for WT development.[9] Our experience is consistent with the approach of those who recommend close observation with ultrasound surveillance every 6 months for a 4-year period, without adjuvant chemotherapy.[2] Given that an ENR may occur from a position as cranial as the chest wall to as caudal as the scrotum, a concurrent primary nephroblastoma or heterotopic nephrogenic rest should be excluded. The clinical behavior of a nephrogenic rest enlarging in size indicates that the lesion may have the potential for a malignant transformation, and imaging is the key to management of this entity.[9] Although contrast-enhanced MRI and CT are considered the best imaging modalities, ultrasonography can detect rests as small as 8 mm in dimension and is the modality of choice for surveillance. Abdominal CT and MRI should follow sonographic detection as part of the workup when a nephrogenic rest is discovered.[7] In our case, however, the parents refused to give their consent either to a CT scan because of the ionizing radiation or to MRI since this modality requires sedation. Only one of the reported cases with an ENR in the inguinal region developed an extrarenal WT at the same site during the follow-up period.[1] Our patient was asymptomatic at 18 months of follow-up and had negative surveillance imaging studies with no evidence of recurrence. Although rare, ENRs should be included in the differential diagnosis of any nodular mass encountered in the inguinal canal. As no specific guidelines for this entity are available, close surveillance with a long-term follow-up is mandatory.

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Diagnosed congenital hypothyroidism with missing follow-up: Is it time for a national registry?

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A treatable and preventable disorder, congenital hypothyroidism (CH) is still a common cause of mental retardation. A 17-year-old Saudi boy with CH due to an ectopic thyroid gland was diagnosed by the neonatal screening program. Thyroxine replacement therapy was started for one month when the family chose to discontinue medication and follow-up. He was not then seen until 11 years of age. Thyroxine was restarted with a close follow-up, although thyroid function tests gradually improved back to normal levels, but his final height was short (159 cm) and IQ was negatively affected. Despite the diagnosis having been made at an appropriate time, patient was lost to follow up. This indicates an obvious flaw in the system for follow-up care. We recommend a registry of patients with CH to monitor their care. The aim of such a registry would be to monitor the efficiency and efficacy of neonatal screening.

Congenital hypothyroidism (CH) is one of the most common treatable and preventable causes of mental retardation.[1,2] Its incidence worldwide is approximately 1 in 3000 to 4000 live births.[3,4] In the Saudi population, the incidence of permanent CH diagnosed by routine neonatal screening in the Najran health region (Southern Province) has been reported to be 1 in 1400 newborn infants,[5] a figure far higher than that reported in other regions of Saudi Arabia and worldwide. The incidence in Riyadh is 1 in 2666.[6] Reports from other regions of Saudi Arabia suggest that the incidence of CH is 1 in 2500 to 3500.[7-9] These figures are comparable with the worldwide incidence of CH. The high incidence of CH in the Saudi population supports the need for a neonatal screening program.

Newborn screening in Saudi Arabia started as an individual program, initially in ARAMCO in 1987-1988, and 2 years later in National Guard hospitals. In 1985, it was started in a military hospital[9,10] followed by the Ministry of Health in 1989, and in King Saud University and private hospitals in 1992.[6,11] The screening in these programs was not mandatory, and no monitoring happened at the national level.

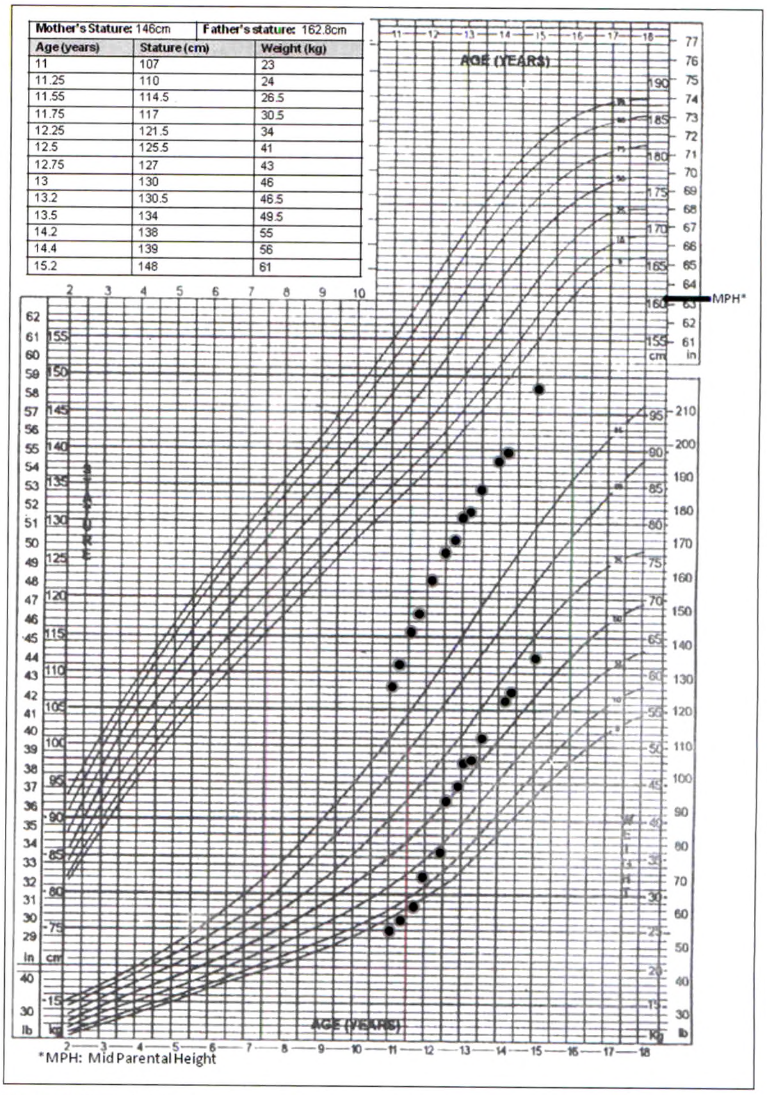
Since the development of pilot screening programs for CH in Quebec, Canada, and Pittsburgh, United States in 1974, newborn screening for CH has become a routine in almost all developed countries.[12] These newborn screening programs are excellent, function efficiently, and achieve their objective of diagnosing a common cause of preventable mental retardation. Certainly, the main objective of screening is the eradication of mental retardation after CH has been diagnosed. In addition to the profound clinical benefit of screening, it has been estimated that the cost of screening for CH in newborns, 12 Saudi Riyals per each test, is much lower than the cost of treating CH diagnosed at an older age.[2,13] Any newborn screening program should include screening, follow-up, diagnosis, management, system evaluation, and education. Without proper follow-up and education, newborn screening programs will fail.[2,14] The aim of such a registry is to monitor the efficiency and efficacy of neonatal screening, provide disease surveillance, and allow identification of possible etiological risk factors for the disease.[13]

CASE

A 17-year-old Saudi boy with CH due to an ectopic thyroid gland was diagnosed by the neonatal screening program. His cord thyroid stimulating hormone (TSH) was 373 mIU/L, and his free thyroxine (FT4) was 10.4 pmol/L. A repeat serum thyroid function test revealed a TSH of >196 mIU/L, FT4 of 9.1 pmol/L, and FT3 of 4.4 pmol/L. Thyroid microsomal and thyroglobulin antibodies were both negative. His thyroglobulin level was 223 ng/mL (<60), and his thyroxine binding globulin was 27 µg/ml (12-28). A thyroid scan and uptake showed the presence of ectopic, sublingual thyroid tissue with an uptake of 1.8%. The patient was immediately started on the thyroxine replacement therapy after confirming the diagnosis, but unfortunately the parents discontinued L-thyroxine after the first neonatal visit at 1 month of age. This lasted for 11 years. At that time, he presented to the pediatric endocrine clinic in a tertiary hospital with complaints of short stature and poor school performance.

At presentation, he had coarse facial features and dry yellow skin with normal sclera. His growth parameters were both below the 5th percentile (**Figure 1**). His height was 107 cm (24 cm below the 5th percentile), and his weight was 23 kg. His father's and mother's heights were 162.8 cm and 146 cm, respectively, giving a mid-parental height of 160.9 cm. His TSH value was 585 mIU/L (0.4-5.5) and his FT4 was low at 3.7 pmol/L (11.5-23.2). His fasting lipid profile demonstrated a cholesterol level of 10.5 mmol/L (3.1-5.2), triglycerides of 1.9 mmol/L (0.15-1.4), low density lipoprotein of 7.3 mmol/L (1.3-4.0), and very low density lipoprotein of 0.9 mmol/L. Renal and liver function tests were both normal, apart from an elevated aspartate amino transferase level of 54 U/L (15-37). His cortisol level was normal, and his prolactin level was high at 57.4 µg/L (2.1-17.7).

His bone age was delayed by 4 years, with a standard deviation of 6.6 months, and a pituitary gland MRI showed a pituitary macroadenoma (**Figure 2**). An initial IQ assessment using the Stanford Binet Intelligence Scale was 81. The patient was restarted on thyroxine, and the dose was adjusted accordingly. He was followed up closely in the endocrine clinic, and his thyroid function tests and fasting lipid profile gradually improved back to normal. Six months later, a repeat pituitary MRI showed a resolved macroadenoma, and a repeat IQ assessment gave a score of 83. On follow-up, the patient remained euthyroid. His growth velocity was normal, and his puberty assessment at the age of 16 years showed Tanner stage 5 and the final height at 17 years was 159 cm.



Mother's Stature: 146cm	Father's stature: 162.8cm	
Age (years)	**Stature (cm)**	**Weight (kg)**
11	107	23
11.25	110	24
11.55	114.5	26.5
11.75	117	30.5
12.25	121.5	34
12.5	125.5	41
12.75	127	43
13	130	46
13.2	130.5	46.5
13.5	134	49.5
14.2	138	55
14.4	139	56
15.2	148	61

Figure 1. Growth Chart

DISCUSSION

The transmission of this patient's abnormal test results, with notification of a pediatric endocrinologist, was performed properly, and the follow-up confirmatory testing of serum samples for TSH and FT4 levels was performed to verify the diagnosis. An ectopic, sublingual gland was demonstrated on thyroid radionuclide imaging; thus, a permanent form of CH that requires a lifelong full thyroid hormone replacement therapy with regular medical monitoring and follow-up was diagnosed. The treatment was initiated as soon as the confirmatory blood samples were drawn.

As an infant diagnosed with CH, the patient should be followed in a pediatric endocrinology outpatient clinic at regular intervals and should be monitored clinically for linear growth, weight gain, developmental progression, and overall well-being, with biochemical measurements of his TSH and FT4 levels. His levothyroxine dose should be adjusted according to the patient clinical response and serum TSH and FT4

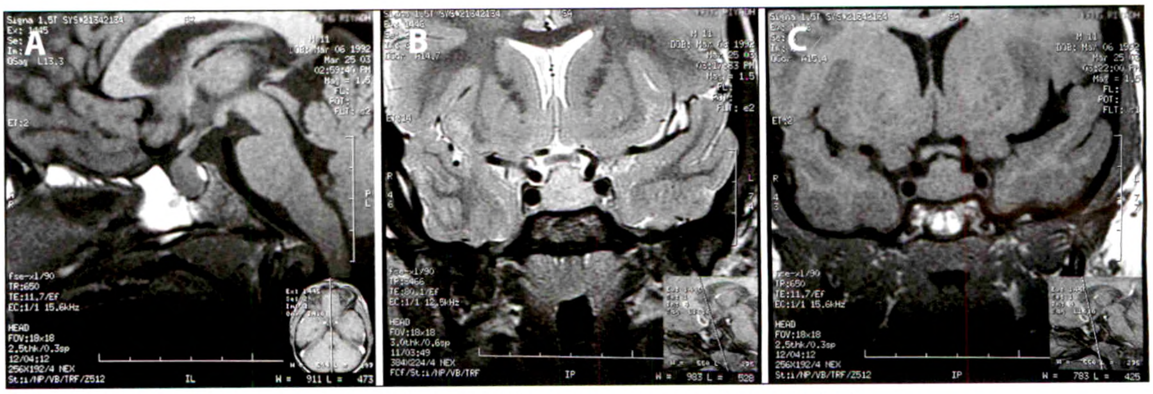


Figure 2. MRI of pituitary gland A) saggital view, B) coronal view, and C) with contrast (coronal view).

levels. Unfortunately, his parents chose to discontinue the therapy and follow-up during early infancy, without consulting the treating physician, until the patient was 11 years of age, when they presented to another tertiary hospital. At that time, the patient had clinical and biochemical evidence of CH as demonstrated by coarse facial features, short stature, learning difficulties, and a low IQ. He had a high TSH level, low FT4, dyslipidemia, and markedly delayed bone age. A pituitary MRI showed a macroadenoma. The patient was started on levothyroxine with a close follow-up at frequent intervals in the clinic. His parents underwent ongoing counseling regarding the importance of adherence to and compliance with medical therapy. On follow-up, he had a normal growth velocity and had entered puberty. His thyroid function tests and fasting lipids normalized, and a repeat pituitary MRI was normal.

The clinical evaluation of an infant with CH should be conducted at frequent intervals during the first 3 years of life, a critical time for brain development when thyroid hormone is crucial. It is essential that follow-up laboratory assessments be obtained in a timely manner and that there be no loss to follow-up if poor compliance is suspected or if abnormal results are obtained.[2] The education of parents by trained personnel with booklets or visual aids is highly desirable. This education should focus on (a) their child's disorder, (b) the etiology of CH, (c) the benefits of early diagnosis in preventing mental retardation, and (d) the potential problems associated with a lack of treatment or inadequate treatment and the benefits of early treatment. Instructions on the appropriate manner in which thyroid hormone is administered and the substances that can interfere with its absorption (e.g., soy, iron, calcium, and fiber) should be included, in addition to guidance regarding adherence to the treatment plan. Lastly, the importance of periodic follow-up care should be emphasized.[2,13]

Because learning problems are possible, even with early diagnosis and treatment, parents should be advised when to seek psychomotor and educational evaluations and interventions. Early childhood intervention programs, if available, should be encouraged.[15-17] In Italy, a National Register of Infants with Congenital Hypothyroidism (INRICH) was established in 1987 that was 10 years after the nationwide newborn screening program started. The study group for CH published their experience for more than 20 years. These studies explain the importance of a registry in providing continuous surveillance of CH. INRICH helps a great deal to characterize the Italian population of babies with CH. It also allows to them to perform a standardization of screening procedures and improvements at the time at starting treatment and in the determining the dose of therapy. Furthermore, the program provides a unique opportunity for research. In general the registry is considered a potent tool of surveillance, epidemiological research, and knowledge on CH.[13] In our patient, although the newborn screening program diagnosed CH and treatment was initiated as early as possible, there was an obvious and clear defect in the system and follow-up care of the patient. We recommend a registry for each patient with CH to recall when a follow-up appointment is missed.

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case report

Perioperative concerns in patients with tumor-induced osteomalacia for surgical excision of tumor

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Tumor-induced osteomalacia (TIO) or oncogenic osteomalacia is a paraneoplastic syndrome, usually associated with mesenchymal tumors. TIO is probably an underreported entity owing to diagnostic and localizing limitations. With improvement in such modalities, patients with TIO are likely to be encountered more frequently in future anesthetic practice. It does not respond to conservative medical management; thus surgical resection of the lesion is the treatment of choice. Anesthetic management of such cases has not been reported in published studies and thus we report two such cases of hypophosphatemia, induced by frontoethmoidal tumors and the anesthetic implications and challenges of such a rare entity. Surgical excision of the causative lesion results in dramatic resolution of symptoms. Vigilant adherence to the pertinent perioperative concerns related to severe hypophosphatemia is crucial to a favorable surgical outcome in these patients.

Tumor-induced osteomalacia (TIO) or oncogenic osteomalacia is a paraneoplastic syndrome characterized by hypophosphatemia, hyperphosphaturia, and a low 1,25-dihydroxy vitamin D level resulting in multisystemic manifestations.[1] It is usually associated with mesenchymal tumors secreting a humoral factor (FGF-23), a member of fibroblast growth factor family, which inhibits reabsorption of phosphate through the proximal renal tubule by down-regulation of type IIA sodium phosphate cotransporter.[2,3] TIO is commonly associated with tumors that are located in the craniofacial region and in the extremities; hence localization can be done with the help of a CT scan, MRI, octreotide scan, and positron emission tomography (PET) scan.[4-6] A mixed connective tissue-type phosphaturic mesenchymal tumor comprises approximately 70% to 80% of the tumors associated with TIO and reportedly involves the paranasal sinuses in 6.2% of cases.[7] It does not respond to conservative medical management; thus surgical resection of the lesion is the treatment of choice.[4-6] We tried to focus on the anesthetic concerns in patients with TIO based on our recent experience of two such cases.

CASE 1

A 51-year-old Indian male presented to the department of endocrinology and metabolic diseases at our institute with complaints of generalized body ache and muscle weakness for the past 2 years. The progressive muscle weakness was more in the proximal muscles and gradually led to an inability to bear weight. Serum biochemistry revealed normal calcium and parathormone levels with severe hypophosphatemia (phospahate, PO4 level 1.2 mg/dL) and a high level of serum alkaline phosphatase (770 IU/L [normal range - 20 to 140 IU/L]). Renal parameters were within normal limits. He was started on oral phosphate supplementation (3 g/day), but without significant clinical and biochemical improvement even after 2 weeks. Renal parameters were within normal limits. A CT scan of the thorax and abdomen were normal while MRI of the whole spine revealed a diffuse bulge of the disk annulus at L4-5 and L5-S1 levels with minimal thecal indentation. The PET scan using 18F-FDG (fluoro-deoxyglucose) revealed active uptake by a soft-tissue mass lesion in the left anterior ethmoidal sinus. A provisional diagnosis of tumor-induced osteomalacia was established. Hence ethmoidectomy was planned for this patient. We reviewed the history and tests and focused on manifestations of hypophosphatemia perioperatively. The patient had severe proximal myopathy and respiratory muscle weakness manifested by poor coughing ability and decreased breath holding time of 11 seconds. There was no cardiovascular or neurological involvement. Airway examination was within normal limits. Based on severe restrictive pulmonary disease based on clinical findings and a pulmonary function test, the possibility of postoperative ventilatory support was explained to the patient and consent was taken. Oral phosphate supplementation was continued until the day of surgery. On the day of surgery the patient was shifted in the operating room and monitors including electrocardiography (ECG), pulse oxymetry, noninvasive blood pressure, end-tidal carbon dioxide, and a neuromuscular monitor were attached. Temperature and urine output were also monitored. Anesthesia was induced with intravenous thiopentone 200 mg and fentanyl 100 µg, and endotracheal intubation was facilitated by administering atracurium 25 mg. Anesthesia was maintained with isoflurane 1% in O2/N2O (50:50) (MAC 1–1.2), fentanyl [1 µg/(kg/hour)], and neuromuscular monitor-guided atracurium boluses. The surgery lasted for 3 hours with a blood loss of approximately 600 mL, which was replaced with a balanced salt solution. At the end of the surgery, residual neuromuscular block was reversed and the trachea was extubated after the TOF ratio exceeded 0.9. The patient was conscious, pain-free, and normothermic, and was monitored overnight in the high-dependency unit. In the first postoperative week, clinical symptoms and serum biochemistry improved dramatically-serum PO4 levels became 2 .8 mg/dL (normal, 2.5-4.5 mg/dL) on the postoperative day 2 itself, and muscle weakness gradually resolved.

CASE 2

A 45-year-old Indian male presented with bone pain, nasal obstruction, and proximal muscle weakness for 7 years, which progressively worsened and he was almost bedridden for the last 1 year. He was operated on for suspected rhinosporidosis of the left nostril 8 years back, which on histopathologic examination revealed hemangiopericytoma. He also had a history of pathological fractures of the right humerus and left femur following trivial trauma. He was receiving oral phosphate supplementation (NaH2PO4 + Na2HPO4) 3 g/day with no symptomatic improvement. The biochemical investigation revealed a low serum PO4 (1.4 mg/dL), a decreased ratio of maximum rate of renal tubular reabsorption of phosphate to glomerular filtration rate (TmPO4/GFR), similar to that in the previous case, and a high level of serum alkaline phosphatase (480 IU/L [normal range: 20-140 IU/L]). MRI revealed a recurrent mass in the left nasal cavity with intracranial extradural extension into the frontal and sphenoid sinus. A pulmonary function test revealed a combined restrictive and obstructive pulmonary disorder (FVC [forced vital capacity) 49%, FEV1 [forced expiratory volume in second] 50%, PEFR [peak expiratory flow rate] 65% of predicted value). A similar anesthetic technique as that of case 1 was followed in this patient with a special emphasis on careful positioning during induction and while shifting him postoperatively.

DISCUSSION

In both our patients, TIO was associated with mesenchymal tumors of the paranasal sinuses. Increased renal excretion of phosphorus was noted based on the decreased value of the maximum transport of PO4 in the renal tubules relative to the glomerular filtration rate (TmPO4/GFR) (0.5 mmol/L, normal range 0.8-1.4 mmol/L). Parathyroid hormone (PTH) being the chief physiologic regulator of renal reabsorption of phosphate, the detection of normal PTH levels with decreased tubular reabsorption of phosphorus prompted the search for ectopic causes. A skeletal survey and bone scan suggested a metabolic bone disease with multiple pseudofractures in ribs and bilateral subtrochanteric regions.

Moderate-to-severe hypophosphatemia is the hallmark of TIO and can potentially result in multiple organ dysfunction primarily because of a decrease in intracellular adenosine triphosphate and 2,3-diphophoglycerate.[8] These changes are of great concern in the perioperative management of these patients for any surgical procedures. Hypophosphatemia has been implicated as a cause of rhabdomyolysis, chronic myopathy, respiratory failure, hemolysis, osteomalacia, and left ventricular dysfunction. Untreated severe osteomalacia may lead to pathological fractures of the vertebrae and ribs, resultant chest wall deformity, and respiratory compromise.[1] Decreased diaphragmatic contractility, low maximal inspiratory pressure, or low maximal expiratory pressure and failure in weaning from ventilatory support has been attributed to hypophosphatemia.[9] Also, hyperventilation with resultant respiratory alkalosis and infusion of dextrose-containing fluid exacerbates hypophosphatemia by stimulating movement of phosphorus into cells. It also leads to reversible cardiomyopathy and ventricular arrhythmias, and may also induce an impaired response to vasopressor agents.[10] Hypophosphatemia is associated with impaired glucose metabolism in both hyperglycemic and euglycemic states. This effect is primarily a reflection of decreased tissue sensitivity to insulin. Hemolytic anemia and reduced chemotaxis and leukocytic bactericidal activity have also been reported in hypophosphatemia.[10] The neurologic sequelae of severe hypophosphatemia include central and peripheral neuropathy, central pontine myelinolysis, seizures, and coma. A severe neuropathy resembling Guillain-Barré syndrome has also been reported recently.[11] TIO is characterized clinically by adult-onset bone pain, muscular weakness, and multiple fractures with dramatic recovery after complete resection. All these manifestations of hypophosphatemia and possible complications from phosphate supplementation are of concern to anaesthesiologists when a patient with TIO presents for surgical resection.[9] Positioning of the patient during movement to the operating room and induction of anesthesia in the perioperative period should be done with utmost caution because of severe osteomalacia, the risk of pathological fractures, and skeletal deformities. This is also implicated during positioning for regional anesthetic techniques and hence feasibility should be assessed in the preanaesthetic evaluation. Based on the severity of respiratory compromise, postoperative ventilatory assistance should be anticipated. However, both our cases could be extubated in the operating room. Features of cardiomyopathy and ECG changes suggestive of arrhythmias should be noted preoperatively, and the need for invasive monitoring may be anticipated. These were not present in our cases. Peripheral neuropathy should also be documented prior to regional anesthetic procedures.

TIO is probably an underreported entity owing to diagnostic and localizing limitations. With improvement in such modalities, patients with TIO are likely to be encountered more frequently in future anesthetic practice. Vigilant adherence to the pertinent perioperative concerns related to severe hypophosphatemia is crucial to the favorable surgical outcome in these patients.

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what's your diagnosis?

An uncommon cause of duodenal obstruction

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A 30-year-old female patient presented to the gastroenterology outpatient department with complaints of anorexia, weight loss and vomiting off and on for the previous 6 months. There was no history of jaundice or diabetes. The patient had mild pallor but her vital signs were within normal ranges. Ultrasound of the abdomen revealed gross distension of the stomach and the proximal part of the duodenum. A barium meal was followed by contrast enhanced computed tomography.

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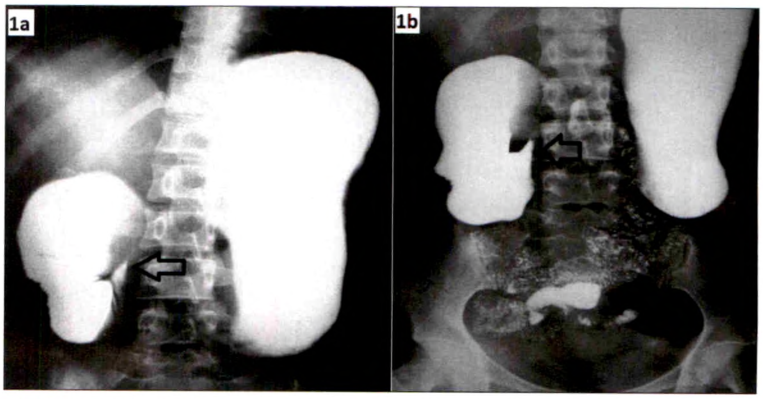

Figure 1. Barium meal shows dilated stomach and duodenum with sudden narrowing of the third part of the duodenum (arrow). Delayed image (1b) shows minimal distal passage of contrast but persistent narrowing with proximal dilatation.

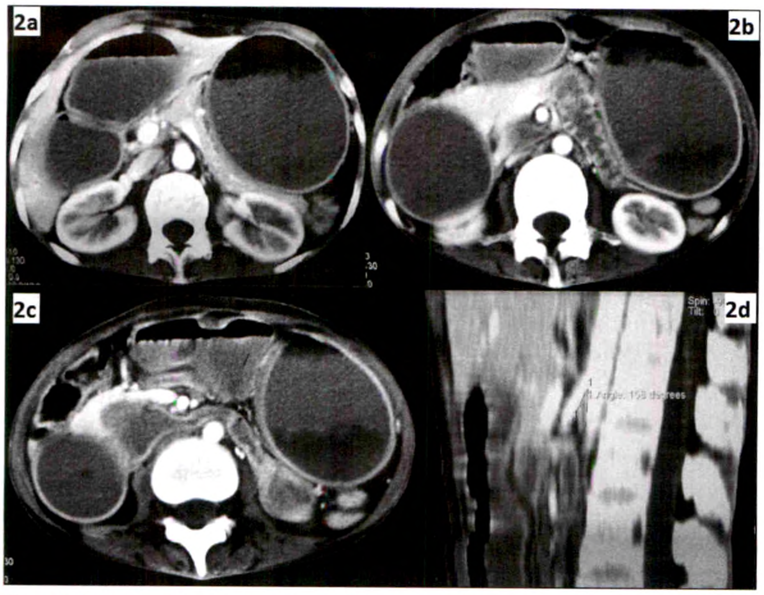

Figure 2. Contrast-enhanced computed tomography of the abdomen shows dilated stomach, first and second part of duodenum with transition point in the third part of duodenum. CT scan also rules out any luminal or intrinsic cause of compression. Sagittal reconstruction (2d) shows decreased aortomesenteric angle to 22°.

Sclerosing encapsulating peritonitis with perforation of the gastrointestinal tract: a serious complication of continuous peritoneal dialysis

To the Editor: Sclerosing encapsulating peritonitis (SEP) is one of the most serious complications of peritoneal dialysis. It is characterized by partial or intermittent bowel obstruction and survives subsequent high morbidity and mortality.[1] A 36-year-old female patient was admitted to the nephrology department with a 24-hour history of abdominal pain and intermittent vomiting. The patient had had chronic renal failure with right renal agenesis for 13 years. SEP was established 8 months previously, and peritoneal dialysis, performed for a long period, was stopped. The general surgery department was consulted. On physical examination, a tender lump was palpated in the umblical region of the abdomen with mild muscle guarding and rebound tenderness. Plain abdominal x-ray showed dilated loops of small bowel with air-fluid levels and free gas under the diaphragm. Abdominal ultrasonography revealed dilated bowel loops, especially in the center of the abdomen. There were localized fluid collections in whole recesses. At laparotomy, 400 mL of purulent fluid was aspirated. A fibrous capsule covering all abdominal viscera was revealed (**Figures 1 and 2**). The liver, stomach, appendix, small bowel loops, as well as the whole colon were also covered with this fibrous capsule, which appeared like a cocoon. Dissection of adhesions from other was impossible. Although we tried to find the perforation, we could not find it because of extensive adhesions and the fragility of the tissues. Histology of the peritoneal membrane showed thickened fibrocollagenous tissue with chronic non-specific inflammation. An enterocutaneous fistula developed on the fifth postoperative day. The patient died from sepsis 3 weeks after the operation.

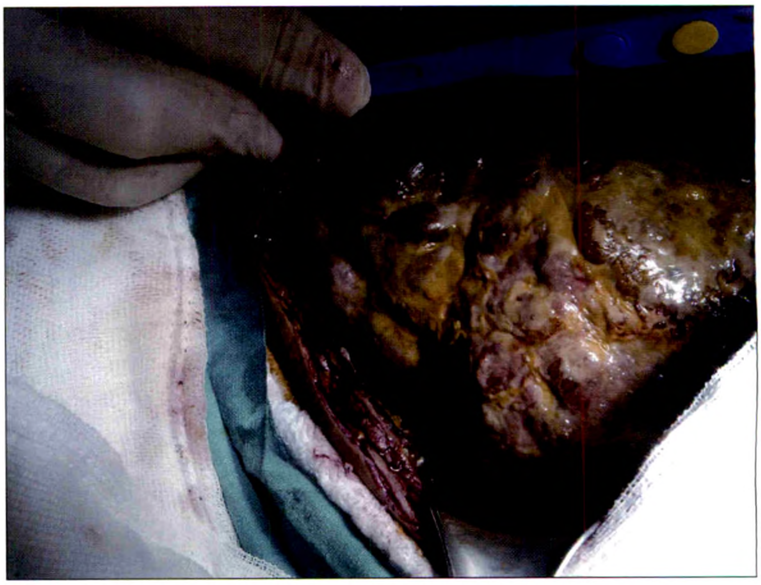

Figure 1. The fibrous capsule covering all abdominal viscera.

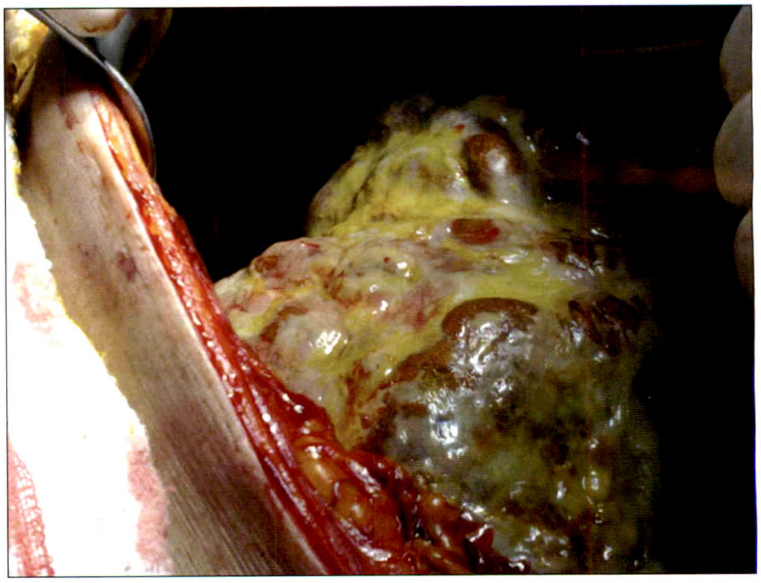

Figure 2. The fibrous capsule covering all abdominal viscera.

SEP is rare. The idiopathic form (also known as abdominal cocoon) was first described by Foo et al in 1978.[2,3] It is characterized by a thick grayish-white fibrotic membrane, partially or totally encasing the small bowel.[4] The fibrocollagenic cocoon sometimes extends to involve other organs such as the colon, liver and stomach. Clinically, it presents with recurrent episodes of acute, subacute or chronic small bowel obstruction, weight loss, nausea and anorexia, and sometimes with a palpable abdominal mass, but some patients may be asymptomatic.[5] SEP can be classified as idiopathic or secondary. The secondary form of SEP has been reported to occur in association with peritoneal dialysis. Other rare causes include use of beta-blockers, abdominal tuberculosis, ventriculoperitoneal and peritoneovenous shunts, liver transplantation, systemic lupus erythematosus, cirrhosis of the liver, carcinoid syndrome, familial Mediterranean fever, asbestos exposure and recurrent peritonitis. The initial symptoms directly depend on disorders of the gastrointestinal tract. Despite the distinctive clinical findings strongly supporting a diagnosis of SEP, a radiologic examination is required to establish the clinical diagnosis of SEP. Laparotomy or laparoscopy is required to confirm the diagnosis. The key points in conservative treatment are early diagnosis, cessation of peritoneal dialysis with transfer to hemodialysis, sustained bowel rest with total parenteral nutrition, and corticosteroids. In the literature, there is no consensus for the treatment of SEP.[1,5]

It is very important to establish diagnosis before development of life-threatening complications of SEP such as intestinal obstruction and perforation because of high morbidity and mortality rates. Prevention and early diagnosis become even more important.

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Capecitabine-induced terminal ileitis

To the Editor: Capecitabine (Xeloda, Roche) is an oral fluoropyrimidine prodrug which is a valuable substitute for parenteral 5-flourouracil (5-FU) for the treatment of colon cancer and metastatic breast cancer.[1] In comparison with intravenous 5-FU, capecitabine was associated with less frequent diarrhea (47.7% vs 58.2%), neutropenia and stomatitis.[2] These features have contributed to the increased use of capecitabine. There are two published case reports describing small bowel toxicity associated with capecitabine.[3,4] We report a patient with terminal ileitis secondary to the use of this drug. This is the first reported case which was reversible, isolated and proven by endoscopy and histology.

The patient was a 65-year-old Saudi male diagnosed with locally advanced and metastatic adenocarcinoma of the rectum. He received pelvic radiation therapy of 30 Gy given in 10 fractions over 2 weeks to control his pelvic disease. He was subsequently started on XELOX (capecitabine plus oxaliplatin) chemotherapy 4 weeks after finishing the radiation therapy. The dose of capecitabine was 1500 mg orally twice daily for 14 days every 21 days.[5] This was equivalent to almost 2/3 of the standard dose. Twelve days after the start of this chemotherapy, he was admitted with fever, abdominal pain, vomiting and diarrhea. Initially, he was treated with broad spectrum IV antibiotics and fluids. Capecitabine was discontinued. Stool for *Closteridium difficile*, parasites and culture were all negative. His course was prolonged and colonoscopy showed an isolated ulceration in the terminal ileum (**Figure 1**). The histopathology was consistent with inflammatory changes and eosinophilic infiltrate but no evidence of malignancy or granulomas (**Figure 2**). His condition improved with conservative treatment. The dihydropyrimidine dehydrogenase (DPD) mutation test was negative. A repeat colonoscopy 2 months later did not show any residual abnormality. He subsequently received a second cycle of XELOX chemotherapy 5 weeks after this first cycle, but the dose of capecitabine reduced to 1000 mg twice daily. He tolerated this well with no recurrence of gastrointestinal toxicity. He continued to respond and tolerated the treatment well.

Most patients tolerate capecitabine well. However, a number of patients develop severe and sometimes life-threatening toxicity after standard doses of capecitabine (which is 1250 mg/m^2 orally

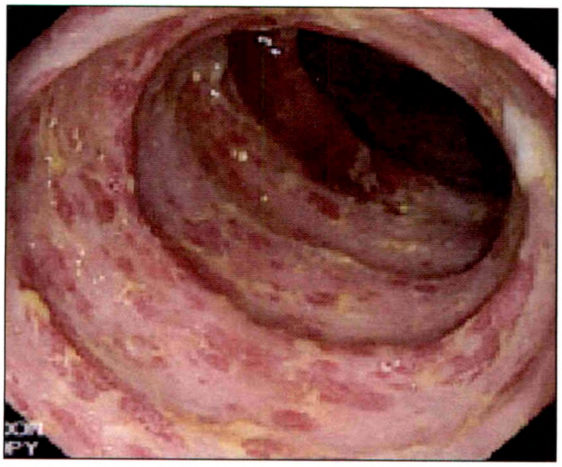

Figure 1. Colonoscopy showed isolated terminal ulceration.

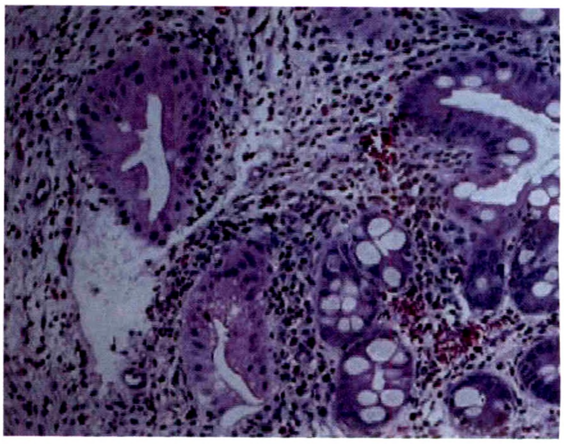

Figure 2. The histopathology was consistent with inflammatory changes and eosinophilic infilterate but no evidence of malignancy, granulomas or CMV (cytomegalovirus).

twice daily for 14 days every 21 days).[5] The major gastrointestinal manifestation of 5-FU cytotoxicity is diarrhea, which may be severe as well as dose-dependent and schedule dependant. However, in the patient described in this report, the colon appeared to be normal with toxicity limited to the the terminal ileum. This toxicity appeared to be dose dependant as there was resolution of the initial complaints and the patient was able to tolerate the treatment without suffering with an appropriate dose reduction. Radiation-induced ileitis was believed less likely to be the cause as the field of radiation exposure was away from the terminal ileum. In addition, there was a gap of 6 weeks between the end of radiation and the onset of the symptoms and a relatively low dose of radiation was utilized (30 Gy over 2 weeks). Finally the symptoms correlated with the dose of capecitabine.

There are very limited reports describing ileitis caused by capecitabine. We found two cases reported separately.[3,4] The first was of a patient receiving single agent capecitabine in the adjuvant setting. Similar to our patient, ileitis was confirmed by endoscopy and histologically. The second patient received XELOX and bevacizumab in the metastatic setting. Terminal ileitis was diagnosed clinically and radiologically without endoscopy examination. To our knowledge, our report describes for the first time a reversible capecitabine-induced terminal ileitis that was confirmed endoscopically and histologically. This complication was successfully prevented from recurrence by reduction of the capecitabine dose in the subsequent cycles. Physicians should be aware of this side effect, which could be life threatening but appears to be dose dependant.

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Hummingbird sign in progressive supranuclear palsy

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Progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) is a neurological disorder characterized by degeneration of the midbrain, basal ganglia and other structures like the frontal lobe, pyramidal tracts and cerebellum. It manifests in middle and late adult age by progressive supranuclear gaze, palsy, postural instability with recurrent falls, mainly in a backwards direction, symmetrical rigidity. frontal lobe features, and dementia.[1] It can be confused with other diseases like idiopathic Parkinson disease, multiple-system atrophy and corticobasal degeneration. To date, the diagnosis of progressive supranuclear palsy is based on clinical grounds. No biomarker has been discovered. The neuroimaging characteristics, particularly the hummingbird sign, is considered quite suggestive of progressive supranuclear palsy.

CASE

A 58-year-old male presented with insidious-onset, progressive difficulty in initiation of, and slowness in execution of movements for the last 5 years. The patient had recurrent falls starting 6 months from onset of symptoms. For the same duration, he had impaired gait and a change in speech. The gait was short shuffling gait with hesitation in initiation and difficulty in walking through narrow passages along with freezing episodes. Speech gradually became slow, low in volume and monotonous in character. Family members noticed impaired cognition. He showed a poor response to a trial of levodopa therapy. There was no history of trauma, stroke-like episodes, hallucinations, fluctuations of clinical symptoms or dysautonomia.

His BP was 169/86 mm Hg with no evidence of postural hypotension. He had a staring look with infrequent blinking and presence of neck dystonia. A mini–mental status examination score was 21/30. He had vertical gaze palsy, hypermetric horizontal saccades and hypometric vertical saccades, impaired optokinetic nystagmus and positive square-wave jerks. There was rigidity in both the upper and lower limbs, and the plantars were bilaterally extensor. Other parameters of neurological examination were essentially normal.

The liver function test did not reveal any abnormality. Hemoglobin was 130 g/L, total leukocyte count was 6500 cells/cu. mm, random blood sugar was 126 mg/dL, and serum creatinine was 1.2 mg/dL. Magnetic resonance imaging T2-weighted image showed atrophy of the midbrain tegmentum with relative preservation of the shape of the pons (**Figures 1, 2**). These images resemble the shape of a hummingbird, and are thus known as the "hummingbird sign."

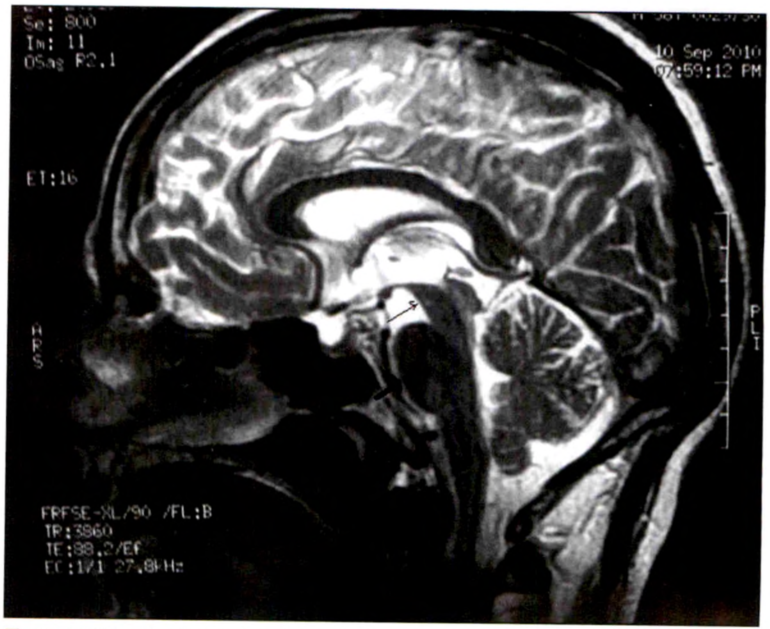

Figure 1. Mid sagittal MRI T2-weighted image revealing midbrain atrophy (thin arrow), and cistern dilatation with preserved pons (thick arrow) resembling a hummingbird.

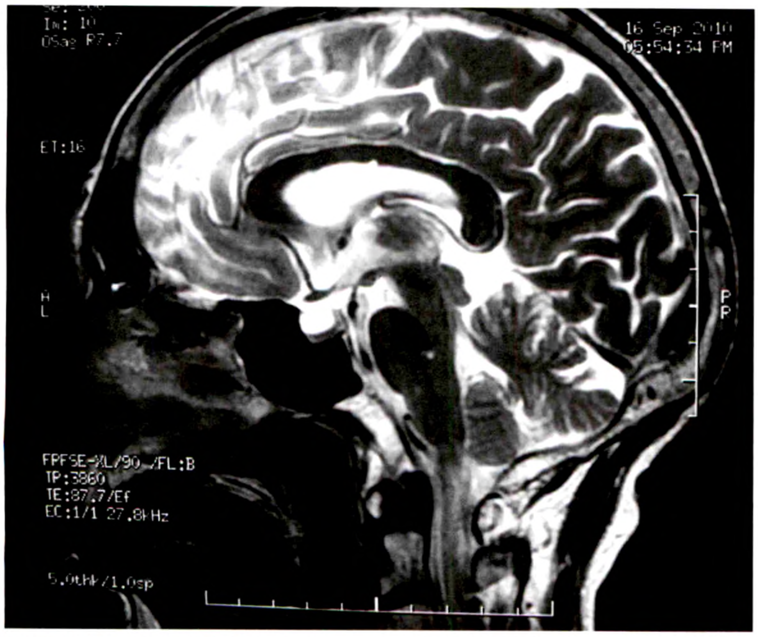

Figure 2. Mid sagittal MRI T2 weighted image of age sex matched control revealing absence of hummingbird sign

DISCUSSION

Progressive supranuclear palsy is a neurodegenerative disorder, mainly affecting eye movements, cognition and posture.[2] Close differential diagnoses of this condition are Parkinson disease, multiple-system atrophy, and corticobasal degeneration.[3] MRI findings of progressive supranuclear palsy are midbrain atrophy with dilated cisterns, thinning of the quadrigeminal plate, third ventricular dilatation and the characteristic hummingbird sign.[4] Using mid-sagittal plain MRI, the hummingbird sign was demonstrated in all progressive supranuclear palsy patients but was negative in Parkinson disease and controls. hummingbird sign in progressive supranuclear palsy patients was due to atrophy of the midbrain and relative lengthening of the interpeduncular fossa and preserved pons.[5] Hummingbird sign on MRI has a sensitivity of around 100%. hummingbird sign on MRI can be a useful diagnostic clue for physicians for confirmation of diagnosis of progressive supranuclear palsy and can help to differentiate from Parkinson disease, which is a treatable neurological disorder.

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retraction notice

The following article is retracted because it was brought to our attention that it was heavily plagiarized from an earlier article published in the Asian Journal of Surgery (Chow et al. Asian J Surg. 2005 Jul;28(3):179-84. PMID: 16024311). Attempts to contact the corresponding author for an explanation were unsuccessful.

The authors are banned from future publication in the *Annals of Saudi Medicine*.

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erratum

In the above article, author first and last names were reversed. They should have appeared as follows:
Awatef Msolly, Olfa Gharbi, Kacem Mahmoudi, Sami Limem, Makram Hochlef, Slim Ben Ahmed

تقييم استخدام والدي أطفال مرضى الربو في عيادات الأطفال للانترنت للحصول على المعلومات الصحية في الرياض، المملكة العربية السعودية

المقدمة والأهداف: ينمي استخدام المرضى للانترنت الوعي بحالتهم الصحية واستخدامه من قبل الأطباء يساعدهم في اتخاذ قرارات مبنية على أدلة. هذه الدراسة تهدف إلى تقييم مدى استخدام الانترنت من قبل والدي الأطفال المصابين بالربو ومصادره و آثاره (الرياض، المملكة العربية السعودية).

التصميم والمكان: دراسة مقطعية جمعت بيانات من عيادتين للأمراض الرئوية للأطفال (خاصة وعامة) لمعالجة الربو في الرياض، المملكة العربية السعودية خلال الفترة ما بين يناير ومايو ٢٠١١م.

المرضى والطرق: تمت الاستعانة بأداة مصممة خصيصاً لجمع بيانات من ٥٠٠ عينة عشوائية من آباء الأطفال المصابين بالربو. هذه الأداة شملت البيانات الديموغرافية (الآباء والأطفال) واستخدام الانترنت (المصادر ومقدار الاستخدام والأهداف).

النتائج: شخصت حالة معظم الأطفال في هذه العينة (٧٧٪) بأنها ربو من قبل الطبيب المعالج (٧٨٪) قبل أن يكملوا الثالثة من عمرهم. من بين الآباء المستخدمين للانترنت (n=٤٠٠)، ٥٣٪ استخدم الانترنت لمدة ١٠ دقائق إلى أقل من ٣٠ دقيقة أو أقل من ١٠ دقائق (٢٢٪). وكانت الأسباب المذكورة لاستخدام الانترنت تشمل الاطمئنان والتوضيح والاستشارة عبر الانترنت والبحث عن خطة جديدة للعلاج أما أسباب عدم استخدام الانترنت فشملت عدم توفر المعلومات باللغة العربية وتوفر معلومات شديدة التخصص. وقد اقترح الآباء توفير الخدمات الالكترونية الآتية: استشارة الطبيب المعالج والتحدث معه، والحصول على معلومات محدثة عن الربو، وخدمة تحديد المواعيد، وتوجيه المستخدم إلى مواقع الكترونية خاصة بالربو. أشار التحليل متعدد المتغيرات إلى أن أهم مؤشرات استخدام الانترنت هي “درجة تعليم مرتفعة لوالدة الطفل’ (OR= ٧,٠٢) تليها “درجة تعليم مرتفعة لوالد الطفل’(OR= ٣,٠٤) و “عدم ممارسة والدة الطفل لمهنة مرتبطة بالقطاع الصحي’.

الاستنتاج: تطبيق نتائج هذه الدراسة قد يساعد الأطباء السريريين في تحقيق تدبير مشترك يتمركز حول الطفل المصاب بالربو.

متابعة ٧١ مريض بداء ويلسون لأكثر من عقدين في مركز للرعاية المتخصصة في المملكة العربية السعودية: مراجعة استعادية.

المقدمة والأهداف: داء ويلسون عبارة عن اضطراب صبغي متنحٍ نادر. ونهدف في هذه الدراسة لوصف الأنماط المختلفة والعلاجات والنتائج لهذا الداء.

التصميم والمكان: دراسة استعادية لمرضى ويلسون استمرت لأكثر من عقدين في مركز للرعاية المتخصصة في المملكة العربية السعودية.

المرضى والطرق: استعادة نتائج الفحوصات المخبرية والسريرية لواحد وسبعين مريض بداء ويلسون من ملفاتهم الطبية وملاحظات الإحالة والسجلات الالكترونية في مستشفانا وتحليلها.

النتائج: متوسط عمر المرضى ١٦,٨ (±١٠,٧) سنة و ٥٦,٥٪ منهم ذكور. وشملت الأعراض الرئيسية لداء ويلسون أعراض كبدية في ٣٩ (٥٤,٩٪) من المرضى وأعراض عصبية في ١٢ (١٦,٩٪) منهم ومزيج من الاثنين في ٢٠ (٢٨,٢٪). لم تظهر أعراض على ١١ (١٥,٥٪) حالة وتم التعرف عليها من خلال فحوصات التحري. وكان تاريخ الأسرة إيجابياً لداء ويلسون في ٤١ (٥٧,٧٪) من الحالات ويظهر زواج الأقارب في ٢٦ (٣٦,٦٪) منها. بلغ متوسط فترة المتابعة ٩٢,٢ (٧٢,٩) (مدى. ١–٣٢٠) شهراً. توفى ١٠ (١٤,١٪) من المرضى خلال فترة المتابعة واستمر ٤٥ (٦٣,٤٪) منهم في المتابعة بينما توقف ١٦ (٢٢,٥٪) عن المتابعة. بلغ متوسط عمر المرضى عند انتهاء المتابعة ٢٥,٣ (١٢) (المدى. ٤–٦٢) سنة. تم اكتشاف ورم كبدي في ٥ (٧,٠٪) من المرضى.وتمت معالجة ٥٨ (٨١,٧٪) من المرضى بعلاج بنسيلامين و٣٢ (٤٥,١٪) بالزنك و١١ (١٥,٥٪) بعقار ترينتاين. خضع ١٦ (٢٢,٥٪) من المرضى لزراعة الكبد وتوفيت حالة واحدة (١,٤٪) وهي على لائحة الانتظار. حالة الكبد كانت مستقرة أو متحسنة في ٣٥ (٤٩,٣٪) من المرضى. تحسن الوضع العصبي ل١١ (٣٤,٤٪) من ٣٢ حالة أصيبت بأعراض عصبية.

الاستنتاج: شملت هذه الدراسة أكبر مجموعة من مرضى داء ويلسون في الشرق الأوسط. وتبين أن أعراض ونتائج داء ويلسون متنوعة جداً ولا يزال يعتمد تشخيصه على أدلة سريرية ومخبرية وإشعاعية لاضطراب في استقلاب النحاس. وينبغي أخذ داء ويلسون في عين الاعتبار عند تشخيص المرضى (بكافة أعمارهم) الذين يعانون من شذوذات كبدية و/أو عصبية غامضة.

أسباب الوفاة في شهادات الوفاة للبالغين: دراسة عرضية المقطع استكشافية في مستشفى جامعي في الرياض

المقدمة والأهداف: التعرف على أكثر أسباب الوفاة شيوعا كما هي مذكورة في شهادات الوفاة للبالغين، وتقييم مدى اكتمال شهادات الوفاة في واحد من أقدم المستشفيات التعليمية في المملكة العربية السعودية.

التصميم والمكان: دراسة عرضية المقطع أجريت في مستشفى الملك خالد الجامعي في الرياض، المملكة العربية السعودية، خلال سنة ٢٠٠٨م.

المرضى والطرق: تمت مراجعة جميع شهادات الوفاة الصادرة في سنة ٢٠٠٨م والتحقق من البيانات بواسطة مراجعين اثنين. تم ترميز أسباب الوفاة حسب نظام ترميز تم تصميمه لهذا الغرض.

النتائج: كان متوسط سن الوفاة (الانحراف المعياري) ٦٣٫٩ (٢٠٫٧). أكثر من ٨٠٪ وصلوا أحياء إلى المستشفى. من بين شهادات الوفاة البالغ عددها ٤١٠ شهادة كان تصنيف السبب الأول للوفاة “غير ملائم’ بنسبة ٦٢٫٢٪، وكان هذا التصنيف أكثر تكرارا بقليل ولكن بدرجة مهمة بين النساء. أما سبب الوفاة الأول الأكثر شيوعا المذكور بصورة ملائمة فهو الورم الخبيث من أي نوع (٧٫٣٪). تليه أمراض القلب الإقفارية (٤٫٩٪). وأما الحوادث والكسور فكانت أكثر شيوعا لدى الفئات العمرية الأصغر سنا ولدى الرجال.

الاستنتاج: هذه أول دراسة توثق الفجوات الممكنة لدى اختصاصيي الرعاية الصحية في المملكة العربية السعودية في فهمهم للوفاة وشهاداتها على أساس التقييم السريري للمتوفى. وهذه النتائج تحتاج إلى التحقق منها بإجراء دراسات مماثلة من قبل قطاعات الرعاية الصحية الأخرى. غير أنه من الواضح أن هناك حاجة شديدة لتدخلات قانونية ومرتبطة بالنظام التعليمي مثبتة لتحسين دقة شهادات الوفاة وذلك إذا ما أردنا تحديد أولويات الرعاية الصحية بصورة صحيحة.

التهاب العظم والنقي متعدد البؤر المعاود المزمن

المقدمة والأهداف: التهاب العظم والنقي متعدد البؤر المعاود المزمن هو اضطراب التهابي طاهر مجموعي نادر يؤثر في مواقع مختلفة ولا تزال أسبابه الإمراضية غير معروفة حتى الآن. وفي حدود معرفتنا، فليس هناك إفادات عن التهاب العظم والنقي متعدد البؤر المعاود المزمن في المملكة العربية السعودية. ونصف في دراستنا هذه، المعالجة والسمات السريرية والمعملية لمجموعة من أطفال التهاب العظم والنقي متعدد البؤر المعاود المزمن.

التصميم والمكان: مراجعة استعادية لمجموعة من المرضى أحيلوا إلى قسم الأمراض الرثوية للأطفال في مركز رعاية اختصاصية، بالرياض في المملكة العربية السعودية.

المرضى والطرق: شخص التهاب العظم والنقي متعدد البؤر المعاود المزمن بناء على التهاب النقي والعظم المعاود مع دليل شعاعي على وجود المرض في موقعين في غياب أي عدوى مسببة لدى طفل يقل عمره عن ١٤ عاماً.

النتائج: بلغ مجموع المرضى في هذه الدراسة تسع إناث وذكر واحد اثنان منهم في مرحلة الرضاعة. وكان تشخيص الإحالة غير دقيق لدى جميع المرضى. شكا جميع المرضى من الألم، وكان لدى ثمانية منهم تورماً وآفات متعددة البؤر. وأظهرت نتائج التصوير مشاهدات تتوافق مع التهاب العظم والنقي المزمن. كما أكدت الفحوصات النسجية والميكروبيولوجية نتائج التشخيص لدى تسعة مرضى. وحقق التسريب الدوري للباميدرونات تحسناً جيداً عند ستة مرضى.

الاستنتاج: كانت هناك غفلة عن التهاب العظم والنقي متعدد البؤر المعاود المزمن في مجتمعنا. وهناك حاجة للتشخيص والعلاج المبكر لتفادي المضاعفات المحتملة.

مكونات المتلازمة الاستقلابية لدى الأطفال المصريين الذين يعانون من السمنة

المقدمة والأهداف: السمنة من أحد المشاكل الصحية العالمية الأكثر خطورة. تهدف الدراسة إلى تقييم العلاقة بين السمنة والمكونات المختلفة للمتلازمة الاستقلابية بين الأطفال السمان في المدارس الذين تتراوح أعمارهم بين ٧ إلى ٩ سنوات وتحديد الخصائص السريرية والكيميائية الحيوية المرتبطة.

التصميم والمكان: دراسة عرضية المقطع بين الأطفال الذين يراجعون لدى العيادات الخارجية في مستشفى الزهراء في شهر مارس ٢٠١٠م.

المرضى والطرق: شملت الدراسة ٦٠ طفلاً يعانون من السمنة (٢٨ ولد و٣٢ بنت) و٥٠ من المجموعة الشاهدة لا يعانون من السمنة (٢٥ ولد و٢٥ بنت). قمنا بفحص القِياسات البَشَرِيَّة، غلوكوز الصائم، تركيزات الأنسولين، مجموع الكولسترول، البروتين الشحمي رفيع الكثافة، البروتين الشحمي خفيف الكثافة، ثُلاثِيِّ الغليسيريد، وضغط الدم الانقباضي والانبساطي. تم تحديد مقاومة الأنسولين عن طريق نموذج تقييم الاسْتِتْباب لمقاومة الأنسولين (HOMA-IR). وقد تم قياس سماكة الدهن تحت الجلد والحشوي باستخدام تخطيط الصدى. حُددت المتلازمة الاستقلابية وفقاً لمعيار “كوك’.

النتائج: تم اكتشاف المتلازمة الاستقلابية في ٢٥٪ من حالات السمنة. وجدنا أن لدى الأطفال السمان قيماً أعلى بشكل واضح في كل من محيط الخصر، نسبة الخصر إلى الورك، مستويات ضغط الدم الانقباضي والانبساطي، الأنسولين، نموذج تقييم الاسْتِتْباب لمقاومة الأنسولين و البروتين الشحمي خفيف الكثافة مقارنة بالمجموعة الشاهدة. كان لدى الأطفال السمان المصابين بالمتلازمة الاستقلابية قيماً أعلى بشكل واضح في منسب كتلة الجسم، سماكة طية الجلد، سماكة الدهن الحشوي، محيط الخصر، ضغط الدم الانقباضي والانبساطي، نموذج تقييم الاسْتِتْباب لمقاومة الأنسولين، الأنسولين وثُلاثِيِّ الغليسيريد مقارنة بالأطفال السمان الذين لا يعانون من المتلازمة الاستقلابية، بينما كانت نسبة البروتين الشحمي رفيع الكثافة منخفضة بشكل واضح. إن معدل انتشار ارتفاع ضغط الدم وخلل الدهون في الدم أعلى لدى الأطفال السمان المصابين بالمتلازمة الاستقلابية مقارنة بالأطفال السمان الذين لا يعانون من المتلازمة الاستقلابية. أظهرت النتائج وجود علاقة ايجابية بين الدهن الحشوي ومحيط الخصر ومستوى الأنسولين في الأطفال السمان.

الاستنتاج: إن نسبة انتشار المتلازمة الاستقلابية واضحة لدى الأطفال المصريين الذين يعانون من السمنة. كانت السمنة في منطقة البطن والقيم العالية في نموذج تقييم الاسْتِتْباب لمقاومة الأنسولين (HOMA-IR) لدى الأطفال السمان من المكونات الأكثر شيوعاً لهذه المتلازمة. تشير الدراسة إلى أن زيادة درجة مقاومة الأنسولين مرتبطة بخطر الإصابة بالمتلازمة الاستقلابية.

بداية مرض كرون من مرحلة الطفولة : تجربة من مستشفى تعليمي جامعي في المملكة العربية السعودية

المقدمة والأهداف: يعتبر مرض كرون مشكلة تشاهد على نحو متزايد في المملكة العربية السعودية. والهدف من هذه الدراسة هو وصف أنماط سريرية للأطفال والمراهقين المصابين بالمرض والذين تمت معاينتهم في مستشفى الملك عبدالعزيز الجامعي في جدة في المملكة العربية السعودية.

التصميم والمكان: أجريت دراسة عرضية المقطع في المستشفى بين شهري يناير ٢٠٠١م ومارس ٢٠١٠م.

المرضى والطرق: تم استرجاع البيانات الخاصة بجميع الأطفال والمراهقين الذين تم تشخيص حالتهم بمرض كرون خلال تلك الفترة في مستشفى الملك عبدالعزيز الجامعي وتحليلها.

النتائج: تم تحديد ٩٦ مريضاً. وكان متوسط العمر عند التشخيص ١١,٣ سنة (بمدى يتراوح بين ٠,١٢ إلى ١٧,٦). وكان خمسون (٥٢,١٪) منهم ذكور. وأربع وستون (٦٦,٧٪) منهم سعودياً. تسعة (٩,٤٪) منهم لديهم قريب من الدرجة الأولى مصاب بالتهاب في الأمعاء. وكانت الأعراض الأكثر شيوعا الإسهال بنسبة (٨٨,٥٪) وفقدان الوزن بنسبة (٨٤,٢٪) وفقدان الشهية بنسبة(٨٠,٢٪). وظهرت علامة واحدة على الأقل من المظاهر خارج معوية لدى ٢٤٪ من المرضى. بينما عاني ٤٢٪ من نقص الوزن و ١٩٪ من قصر القامة. وكان التصنيف الأكثر شيوعاً لفائفي قولوني بنسبة (٣٧,٥٪) تلاه القولوني بنسبة ٣١,٢٪. وعانى ٢٥ مريضاً (٢٦٪) من داء محيط بالشرج. بينما عاني ١٣ (١٣,٥٪) من تضيق و١٥ (١٥,٦٪) من داء نافذ. كما كشفت الاستقصاءات المخبرية عن معاناة ٨٤,٤٪ من فقر الدم، و٥٠٪ من كثر الصفيحات، و٦٤,٦٪ من تدني زلال الدم و٥٠٪ من ارتفاع سُرْعَةُ تثفل الكُرَيَّاتِ الحُمْر، و٥٨,٣٪ من ارتفاع بروتين سي التفاعلي. وقد استجاب ٢٠٪ من المرضى لعلاج (تحريض الهدأة) مع تغذية معوية بينما استفاد البقية من العلاج بالستِيرويدات القِشْرِيَّة.

الاستنتاج: وجدنا أن الأنماط السريرية لمرضى كرون في المنطقة الغربية من المملكة العربية السعودية مشابهة للتقارير الواردة من الغرب.

البِيلَة الكَيلوسِيَّة المحاكية للمتلازمة الكلائية

المقدمة والأهداف: يمكن الخلط بين البِيلَة الكَيلوسِيَّة والمتلازمة الكلائية عند وجود بيلة بروتينية بكمية كبيرة في فحص البول أثناء تقييم البول اللبني/الأبيض. كان هدفنا محاولة تفريق التشخيص في حال وجود بيلة بروتينية كلوية عندما لا يكون هناك دليل واضح على وجود آفة كلوية.

التصميم والمكان: مراجعة استعادية للسجلات الطبية لجميع المرضى الحالين من قسم أمراض الكلية في مستشفى واحد.

المرضى والطرق: حددنا مجموعة فرعية من المرضى تم تشخيصهم بالخطأ بالإصابة بمتلازمة كلائية وتلقوا علاجاً مكثفاً كابتاً للمناعة دون تحقيق أي فائدة وشُخصت إصابتهم فيما بعد بالبِيلَة الكَيلوسِيَّة.

النتائج: تم تحديد ١٢ مريضاً (٨ رجال و٤ سيدات) ويبلغ متوسط عمرهم ٣٤,٥ سنة. كان الكيلوسِ ايجابياً في البول لدى ٨ مرضى فيما كان الكيلوسِ ايجابياً عند ابتلاع دهن الزبدة بالفم في ٤ مرضى آخرين. تم أخذ خزعة من الكلية لـ ٦ من المرضى وتم علاج إصابتهم بداء متغير بسيط.
يعاني ٨ من المرضى من بيلة بروتينية كبيرة كما يشير تاريخهم المرضي إلى تلقيهم العلاج بعقار “Prednisone’. ولكن لم يحقق هؤلاء المرضى أي تحسن سريري. حقق اثنان من المرضى نتائج ممتازة مع ثُنائيُّ إيثِيل كاربامازِين “Diethylcarbamazine’ مع مثبطات الإِنْزِيمُ المُحَوِّلُ للأَنْجِيوتَنْسين فيما تطلبت حالة ٨ من المرضى تَسْتيل بيتادين في الوصلة الناسورية مع نجاح هذا الإجراء في ٦ مرضى. نجحت محاولة التصحيح الجراحي في حالتين فقط.

الاستنتاج: إن الأشخاص الذين يعانون من بيلة بروتينية كلائية مع نسبة دهون طبيعية أو منخفضة ومستويات طبيعية لألبومين المصل ، ولون وطبيعية البول، والتكرار وفحص الكيلوسِ في البول يمكن أن يساعد في تحديد المجموعة الفرعية الكبيرة الذين يجب أن يخضعوا لخزعة للكلية ويتلقون في بعض الأوقات للعلاج الكابت للمناعة، والذي لا يشكل فقط خطراً على الحياة ولكن لا فائدة منه لدى هؤلاء المرضى.

تقييم حجم المبيض بالنظر إلى نتائج دراسة الأنسجة ومستويات الهرمونات الجنسية لدى نساء يعانين من نزيف ما بعد اليأس وثخانة بطانة الرحم

المقدمة والأهداف: كثيراً ما يتزامن اكتشاف فرط تنسج سدَى المبيض مع سرطان بطانة الرحم لدى النساء اللواتي تجاوزن سن اليأس. كان الهدف من هذه الدراسة هو التحقق من ارتباط حجم المبيض بنتائج دراسة الأنسجة ومستويات الهرمونات الجنسية لدى نساء يعانين من نزيف ما بعد اليأس وثخانة بطانة الرحم.

التصميم والمكان: دراسة مراقبة استباقية أقيمت بين مارس ٢٠٠٨م وفبراير ٢٠١٠م.

المرضى والطرق: شاركت في الدراسة تسعون امرأة تعاني من نزيف ما بعد اليأس وثخانة بطانة الرحم (٥ ملم ≥). وقد أجري لهن تخطيط صوتي مهبلي لقياس حجم المبيض، وأخذنا عينات دم لمقايسة الهرمونات الستيرويدية الجنسية، بالإضافة إلى عينات من بطانة الرحم للحصول على تشخيص نسيجي نهائي.

النتائج: وفقاً لنتائج الفحص النسيجي كانت هناك ١٨ حالة سرطان غدي في بطانة الرحم (٢٠٪)، و٢٤ حالة فرط تنسج في بطانة الرحم مع اللا نمطية أو بدونها (٢٦,٧٪). وظهرت النتائج حميدة لدى ٤٨ حالة (٥٣,٣٪). كما كانت العلاقة واضحة بين كبر حجم المبيض وارتفاع منسب كتلة الجسم (BMI≥٣٠) (P=٠,٠٠٢)، والسرطان الغدي في بطانة الرحم (P<٠,٠٠١). بعد ضبط السن ومنسب كتلة الجسم BMI، تبين أن زيادة حجم المبيض في حالة السرطان الغدي مرتبط بارتفاع مستوى الإيستراديُول في المصل (P<٠,٠٠١)، وتيستوستيرون المصل (P=٠,٠٤)، والتيستوستيرون الحر في المصل (P=٠,٠١) مقارنة بالنتائج الأخرى لدراسة الأنسجة.

الاستنتاج: ترابط كبر حجم المبيض لدى النساء اللاتي يعانين من نزيف ما بعد اليأس وثخانة بطانة الرحم بارتفاع الهرمونات الستيرويدية الجنسية في المصل، وهو يعتبر واسم خطورة للإصابة بسرطان غدي في بطانة الرحم.

سمات فشل القلب الإحتقاني لدى المرضى السعوديين ومدى التزامهم بإرشادات المعالجة في مستشفى متخصص بالرياض، المملكة العربية السعودية

المقدمة والأهداف: لا تتوفر إلا معلومات محدودة عن سمات المرضى السعوديين المحليين ممن شُخصوا بفشل القلب الإحتقاني CHF ومدى التزامهم بإرشادات العلاج من المرض. تهدف الدراسة لملء هذا الفراغ.

التصميم والمكان: دراسة مراجعة للمرضى الذين تم علاجهم في مدينة الملك عبد العزيز الطبية في الفترة من ٢٠٠٢م إلى ٢٠٠٨م.

المرضى والطرق: تمت مراجعة السجلات للحالات التي تم تنويمها نتيجة لفشل القلب (ممن تم تحديدهم بفشل القلب الإنقباضي (نسبة التفريغ ‹٥٥٪) و/أو فشل القلب مع الحفاظ على نسبة تفريغ سواء سريرياً أو من خلال تخطيط القلب بالصدى و/أو القسطرة القلبية) أو ممن زاروا قسم العيادات الخارجية بنفس الشكوى.

النتائج: من بين ٣٩٢ حالة فشل قلبي احتقاني، متوسط العمر ٦٧,٨ (١٢,٨) سنه أغلبيتهم ذكور (٥٣,١٪). كان ارتفاع ضغط الدم هو المرض المرافق السائد لدى ٨٤,٩٪ من الحالات، ثم مرض السكري من الدرجة ٢ وفرط شحوم الدم. وتعاني ما يكاد تبلغ نسبته ثلاثة أرباع (٧٣,٧٪) من الحالات من خلل خفيف إلى شديد في وظيفة البطين الأيسر، مع معاناة ٦٨,٥٪ من الحالات من اعتلال عضلة القلب اليمنى الإقفاري. وكان الإلتزام بتوصيات استخدام عقار سبيرونولاكتون Spironolactone وممارسة التمارين وتلقي اللقاحات هو الأقل بنسبة (٣٠,٠٪، ٢٠,٥٪ و ١٥,٢٪، على التوالي).

الاستنتاج: تسلط الدراسة الضوء على مدى الحاجة لتثقيف المرضى ومرافقيهم بشكل سليم لزيادة مدى التزامهم بتناول الأدوية. كذلك تشجيع الأطباء للخضوع لدورات التعليم الطبي المستمر والتدريب لتطبيق التوصيات الحالية بشكل سليم الخاصة بعلاج فشل القلب. وتستدعي الحاجة لإجراء المزيد من الدراسات بمقياس أكبر لصياغة وتفعيل مخطط المعالجة الذي سيوجه للتحديات الحالية التي يواجهها الإختصاصيين السريريين ومرضى فشل القلب الإحتقاني.

استخدام (Viabahn) لعلاج عودة التضيق الفخذي المأبضي بعد تثبيت الإستنت.

المقدمة والأهداف: تعتبر عودة التضيق في الشريان الفخذي المأبضي بعد تثبيت الإستنت أمر شائع بنسبة (٢٠٪-٤٠٪). ويعرقل علاج عودة التضيق معدل سالكية ضعيف. يستخدم استنت مغلف بمادة ePTFE وهو خامل وذو مسام صغيرة جداً لا تسمح بنمو هام للأنسجة. إن استخدام الإستنت (Viabahn) قد يُحسن من معدل السالكية في علاج عودة التضيق.

التصميم والمكان: أُجريت مراجعة استعادية لاستخدام طعوم الإستنت (Viabahn) المغروسة في المرضى المصابين بعودة تضيق الشريان الفخذي المأبضي العرضي خلال الفترة من شهر يناير ٢٠٠٤م إلى شهر ديسمبر ٢٠٠٨م.

المرضى والطرق: قمنا بقياس معدل السالكية الأولي باستخدام التصوير المزدوج بالموجات فوق الصوتية بعد سنة و ٣ سنوات. كما قمنا بفحص معدل السالكية الثانوي والإقفار الحاد في الأطراف والبتر.

النتائج: تم تحديد ٢٧ حالة من المصابين بعودة تضيق الشريان الفخذي المأبضي الذين تم علاجهم باستخدام الإستنت .(Viabahn) وكان متوسط طول الآفة ٢٤,٥ سم. وعانى ٥٢ ٪ من المرضى من انسداد كلي بينما عانى ٣٧٪ من إقفار حرج في الأطراف. وكانت معدلات السالكية الأولية من سنة إلى ٣ سنوات ٨٥,١٪ و ٨١,٤٪ على التوالي. وبلغ معدل السالكية الثانوية ٩٦٪. وكانت جميع حالات عودة التضيق بؤرية في الجزء الداني والقاصي من الحواف ولم يتعرض أي منهم لكسر الإستنت.

الاستنتاج: أظهرت الدراسة وجود سالكية جيدة للطُعم المغلف بمادة ePTFE في الإستنت لعلاج المرضى المصابين بعودة تضيق الشريان الفخذي المأبضي بعد تثبيت الإستنت.§

نوعية الحياة لدى مرضى الديلزة الدموية والصفاقية في المملكة العربية السعودية

المقدمة والأهداف: نوعية الحياة نتيجة مهمة بالنسبة للأطباء والمرضى المصابين بداء كلوي في المرحلة النهائية وتلعب دوراً كبيراً في تحديد الأسلوب المتبع في الديلزة. تهدف هذه الدراسة إلى مقارنة نوعية الحياة بين مرضى الديلزة الدموية ومرضى الديلزة الصفاقية.

التصميم والمكان: دراسة وصفية مقطعية أجريت في وحدات الديلزة التابعة لمركزين للرعاية المتخصصة في المملكة العربية السعودية في الفترة ما بين يوليو ٢٠٠٧م حتى يوليو ٢٠٠٨م.

المرضى والطرق: شارك في الدراسة ٢٠٠ مريض يخضعون للديلزة، ١٠٠ منهم خضع للديلزة الدموية و١٠٠ للديلزة الصفاقية. وقد جمعت البيانات باستخدام استبيان نوعية الحياة في مرضى الداء الكلوي.

النتائج: تشابهت السمات الاجتماعية والديموغرافية في الفئتين. كان المتوسط العمري في مرضى الديلزة الدموية هو ٤٧,٥ (١٣,٨) سنة و ٥١,٠ (١٣,٥) سنة في مرضى الديلزة الصفاقية. المرضى الذكور يشكلون ٥٣٪ من مرضى الديلزة الدموية و٤٣٪ من مرضى الديلزة الصفاقية. متوسط مدة الديلزة ٧٧,٢ (٧٥,٥) شهر في مرضى الديلزة الدموية و٣٤,١ (٢٦,٩) شهر في مرضى الديلزة الصفاقية. متوسط نتيجة نوعية الحياة ٤٩,٥ (١٣,٧) في مرضى الديلزة الدموية و ٦١,٣ (١٢,٤) في مرضى الديلزة الصفاقية. متوسط نتائج نوعية الحياة كانت أعلى بدرجة كبيرة في كل النواحي وفي إجمالي نوعية الحياة في مرضى الديلزة الصفاقية فيما عدا نتيجة نوعية الحياة الجسدية حيث كانت أعلى في مرضى الديلزة الدموية ولكن مقارنة بنتائج مرضى الديلزة الصفاقية لم يكن الفرق الإحصائي كبيراً. أشار تحليل الانحدار المتعدد إلى أن الديلزة الدموية مؤشر سلبي لنتيجة نوعية الحياة مقارنة بالديلزة الصفاقية. كما تبين أن العمر والذكورة ومدة الديلزة مؤشرات سلبية لنتيجة نوعية الحياة.

الاستنتاج: نوعية الحياة لدى المرضى الذين يخضعون للديلزة الصفاقية في المملكة العربية السعودية أفضل من نوعية الحياة لدى المرضى الذين يخضعون للديلزة الدموية. وهذه النتائج تؤكد ما ذكر في أبحاث الدول الأخرى.

مقاومة مضاد الفيروس القهري عند الأطفال السعوديين المصابين بفيروس عوز المناعة البشري الذين لم يستجيبوا للخط الأول من العلاج مرتفع النشاط

المقدمة والأهداف: أدى استخدام خلطة العقاقير المضادة للفيروسات القهقرية (ARV) المعروفة بالعلاج مرتفع النشاط (HAART) إلى تحقيق تحسن مهم في نوعية الحياة ومعدل البقيا الإجمالي عند الأطفال المصابين بفيروس نقص المناعة البشري (HIV). غير أن هذه النتائج تبقى مهددة بظهور مقاومة لهذه العقاقير. وقد سعينا في هذه الدراسة إلى تحليل نمط مقاومة العقار المضاد لفيروس نقص المناعة البشري لدى الأطفال المصابين بهذا الفيروس الذين لم يستجيبوا للخط الأول من العلاج مرتفع النشاط (HAART).

التصميم والمكان: دراسة استعادية قائمة على البيانات التي تعود إلى الفترة الواقعة بين يوليو ٢٠٠٦م ويناير ٢٠٠٩م والمتعلقة بانتشار المقاومة الجينية عند الأطفال الذين تلقوا العلاج مرتفع النشاط (HAART). وعانوا من الفشل الفيروسي HIV RNA ‹ ١٠٠٠ copies/ml في مركز طبي متقدم بالرياض.

المرضى والطرق: قمنا بدراسة خصائص جمهور المرضى وتحليل بيانات المقاومة الجينية لدى الأطفال الذين عولجوا بعقار ARV وعانوا من إخفاق فيروسي.

النتائج: من بين ٢٢ طفلاً خضعوا لفحص المقاومة. كانت نسبة انتشار المقاومة للعقار ٨٦٫٤٪. وكانت نسبة الامتثال غير الملائم لعقار ARV لدى الأطفال الذين أبدوا مقاومة للعقار٩١٪. وتم الكشف عن ٢٤ طفرة ضمن مثبطات البروتياز (Plsand ١٤) في منطقة ترميز المنتسخة العكسية (RT). وتم الكشف عن piM٣٦١ في ٨٠٪ من المستفردات. بينما تم الكشف عن rtM١٨٤v في ٧٠٪ من المستفردات والتي كانت مصحوبة بمقاومة متصالبة إلى حدود اثنين من مثبطات نوكليوزيد على الأقل (NRTI). وتم تمييز مقاومة مثبطات RT اللانوكليوزيدية (NNRTI) السريرية المهمة بواسطة rtK١٠٣N. وكان أفضل تأثر ل ARV هو اللوبينافير لدى فئة PI. لم تكن مقاومة ARV متصاحبة من مناطق جغرافية أو تصنيف مركز السيطرة على الأمراض. أظهر الأطفال موضوع هذه الدراسة استجابة مرضية للعلاج الجيني الموجه وللإرشاد العائلي المكثف.

الاستنتاج: تعتبر مقاومة مضادات الفيروسات القهقرية أمراً شائعاً بين الأطفال السعوديين المصابين بفيروس نقص المناعة البشري الذي عانوا من فشل فيروسي للعلاج النشط HAART. ويعتبر الامتثال غير الملائم سبباً شائعاً لمقاومة مضادات الفيروسات القهقرية عند الأطفال. كانت الطفرات M٣٦١ و M١٨٤V أكثر تواتراً عند NI و NRTI و NNRTI. ويجب الاهتمام بتقييم نتائج الاختبارات الجينية لدى جميع الأطفال الذين لم يستجيبوا للعلاج بغية توجيه الاختيار المستقبلي لعلاجات مضادات الفيروسات العكوسة. مع العلم أن هذه البيانات سوف تساعد في تحسين التدبير السريري للأطفال المصابين بفيروس نقص المناعة البشري في المملكة العربية السعودية.

المدونــات الطبيــة السعوديــة

تصدر المدونات الطبية السعودية مرة كل شهرين عن مستشفى الملك فيصل التخصصي ومركز الأبحاث ، ص.ب ٣٣٥٤ ، الرياض ١١٢١١، المملكة العربية السعودية. يتم توزيع المدونات وإعداد الملخصات العربية بالتعاون مع د. زهير القاوي بواسطة موظفي إدارة الخدمات الإدارية بمستشفى الملك فيصل التخصّصي ومركز الأبحاث. جميع المراسلات والاستفسارات وطلبات الاشتراك ترسل إلى المحرر الأول مكتب المطبوعات (ر.إ ٣٦).

التوزيع:

تُوزع المدونات الطبية السعودية مجانا للأفراد المؤهلين والمؤسسات المؤهلة. المقالات متوفرة أيضا من خلال الإنترنت، الموقع *annsaudimed.net* . إذا كنت ترغب في الحصول على نسخة مطبوعة أرسل رسالة بالبريد الإلكتروني على العنوان *admin@annsaudimed.net* واذكر فيها اسمك، وبريدك الإلكتروني، وعنوانك البريدي، واسم المؤسسة.

الآراء التي ترد في المقالات المنشورة تعبّر عن رأي أصحابها فقط ولا تعبّر عن وجهة نظر المجلة. جميع الحقوق محفوظة للمجلة الطبية. المستشفى لا يؤيد ولا يكفل ولا يضمن ولا يوصي بـ ولا يوافق على أي منتج معلن عنه أو شركة معلنة في المجلة، ويُعلن صراحة أنه لا يتحمل أية مسئولية عن أية أضرار من أي نوع كانت تنشأ عن استعمال أية معلومات ضمن الإعلان أو الإشارة إليها أو الاعتماد عليها. لا يسمح بإعادة طبع أي جزء من المجلة أو نسخه بأي شكل وبأي وسيلة كانت إليكترونية أو آلية، بما في ذلك التصوير والتسجيل أو الإدخال في أي نظام حفظ أو استعادة معلومات بدون الحصول على موافقة من إدارة المجلة.

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